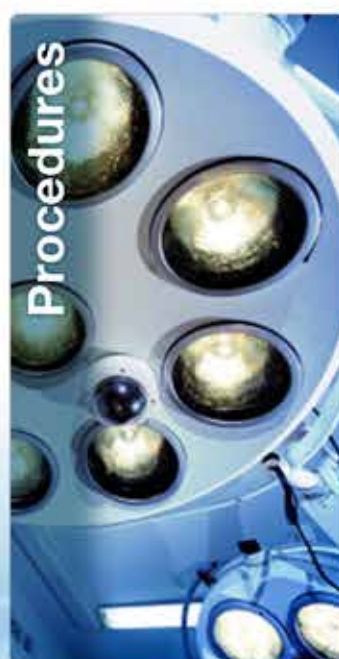
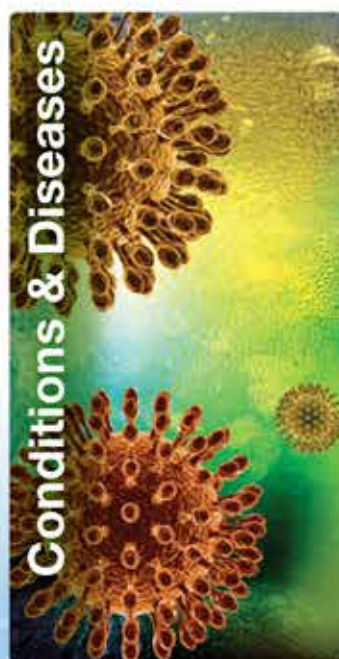


OCTOBER 2014

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accomplishments

IRP researchers have won international recognition and countless awards for research that is truly game-changing—transformational science that advances biomedical knowledge.

The following is a snapshot of some of the IRP's most outstanding research.

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body locations and systems

Brain and Nervous System

2013: Alzheimer's disease: challenging the amyloid dogma

Challenge

The predominant hypothesis for the pathogenesis of Alzheimer's disease suggests that the deposition of fibrillar amyloid in the brain is its causative trigger. However, the repeated failures of Alzheimer's diseases treatment trials targeting amyloid deposition or clearance have highlighted the need to enhance understanding of alternative disease mechanisms.

Advance

IRP researchers led by Madhav Thambisetty, M.D., Ph.D., discovered that a common genetic risk variant for Alzheimer's disease in the complement receptor-1 (CR1) gene is associated with lower brain amyloid burden in at-risk older individuals.

Impact

This study is the first demonstration that a genetic risk factor may mediate Alzheimer's disease pathogenesis by mechanisms distinct from increased deposition of fibrillar amyloid in the brain. The team's findings have highlighted the importance of seeking alternative mechanisms underlying Alzheimer's disease and renew hope that identification of such mechanisms may lead to effective treatments.

Publications

Thambisetty M, An Y, Nalls M, Sojkova J, Swaminathan S, Zhou Y, Singleton AB, Wong DF, Ferrucci L, Saykin AJ, Resnick SM. [The Effect of CR1 on Brain Amyloid Burden during Aging and its Modification by APOE Genotype](#). *Biological Psychiatry*. 2013 Mar 1;73(5):422-8.

Gandy S, Haroutunian V, DeKosky ST, Sano M, Schadt EE. [CR1 and the "vanishing amyloid" hypothesis of Alzheimer's disease](#). *Biological Psychiatry*. 2013 Mar 1; 73(5):393-5.

2013: Finding the key to dendritic spine development

Challenge

Normal brain function requires proper synaptic connections. In schizophrenia, the number of dendritic spines—small protrusions from dendrites that help convey neural signals—is reduced, resulting in impaired neuronal connections and cognition. However, the mechanism behind these changes is unknown.

Advance

IRP researchers led by [Zheng Li, Ph.D.](#), studied a mouse model of schizophrenia and found an age-dependent role for dopamine D2 receptors (D2R) in dendritic spine development. They showed that, in these mice, D2R over-activation during adolescence led to deficient dendritic spines and impairments in neuronal circuits and working memory.

Impact

Dr. Li's research revealed a previously unknown function for D2R in the development of synaptic connections, suggesting that targeted treatments for aberrant D2R activity during adolescence may prevent cognitive impairment.

.....

Publications

Jia J-M, Zhao J, Hu Z, Lindberg D, Li Z. [Age-dependent regulation of synaptic connections by dopamine D2 receptors](#). *Nat Neurosci*. 2013 Nov;16(11):1627-36.

Comment: Yin, DM, Xiong WC, Mei L. [Adolescent dopamine slows spine maturation](#). *Nat Neurosci*. 2013 Nov;16(11):1514-6.

.....

2013: Itching for an answer

Challenge

Despite the universality of itching, scientists do not have a full understanding of what triggers or maintains the sensation. How do itch sensory neurons transmit signals to the spinal cord? And how is an itch distinguished from other sensory qualities, such as temperature or pain?

Advance

[Mark A. Hoon, Ph.D.](#), and Santosh K. Mishra, Ph.D., demonstrated that a single neuropeptide transmitter, Nppb, located in a specific subset of neurons, is the primary mechanism by which itch responses are elicited in mice.

Impact

The team's discovery opens doors to a wider molecular understanding of how itch sensations originate and are processed, which could lead to more targeted treatments for conditions associated with chronic itching, such as eczema and psoriasis.

.....

Publications

Hoon MA, Mishra SK. [The Cells and Circuitry of Itch Responses in Mice](#). *Science*. 2013 May 24;340(6135):968-71.

.....

2012: Fission and fusion to help keep our cells healthy

Challenge

Mitochondria—the subcellular organelles responsible for a cell's energy production and other metabolic functions—can suffer from defects of normal development, which have been associated with neurodegenerative disorders, such as Parkinson's disease.

Advance

IRP researchers led by [Richard Youle, Ph.D.](#), described two normal mitochondrial processes—fission and fusion—that appear to play an important role in ensuring mitochondrial health via a “cut and paste” mechanism that removes and repairs damage resulting from cellular stress.

Impact

The new knowledge of mitochondrial fission and fusion processes may allow researchers to harness the cells' natural repair ability to develop new therapies for both mitochondrial and neurodegenerative diseases.

Publications

Youle RJ, van der Bliek AM. [Mitochondrial fission, fusion, and stress](#). *Science*. 2012 Aug 31;337(6098):1062-5.

2001: Moving toward understanding polyglutamine toxicity

Challenge

Polyglutamine diseases, including Huntington's disease, arise from multiple repeats of the glutamine codon—for example CAGCAGCAGCAG—in a variety of genes. Since these diseases likely share similar mechanisms, a better understanding of how these repeats cause dysfunction could aid in the development of therapies.

Advance

IRP researchers led by [Kenneth Fischbeck, M.D.](#), found that the expanded polyglutamine proteins may act as sticky glue, blocking up their normal clearance process. The excess protein then interferes with a number of nuclear factors important in maintaining genetic stability, causing the cell to enter apoptosis, or programmed cell death. These observations correlate with the neuronal death observed in conditions such as Huntington's disease.

Impact

The finding that polyglutamine toxicity in cell culture may be due to interference with nuclear factors has potential therapeutic implications, and research is underway to evaluate molecules with potential application as disruptors of that process.

Publications

McCampbell A, Taye AA, Whitty L, Penney E, Steffan JS, Fischbeck KH. [Histone deacetylase inhibitors reduce polyglutamine toxicity](#). *Proc Natl Acad Sci U S A*. 2001 Dec 18;98(26):15179-84. Epub 2001 Dec 11.

1970: The first understanding of how brain cells communicate

Challenge

Prior to the 1950s, science knew little about how nerve cells in the brain communicated with each other.

Understanding the signal transmission mechanism was a fundamental challenge to meet before researchers could dive deeper into investigations of brain function.

Advance

For more than five decades, [Julius Axelrod, Ph.D.](#), studied the underpinnings of nerve communication, culminating in his seminal discovery that neurotransmitters—chemical molecules that nerves use to transmit signals—don't just degrade upon reaching their destination, but are re-updated for reuse in later transmissions.

Impact

Axelrod's discoveries revolutionized understanding of how nerve cells communicate, laying a foundation upon which development of many targeted medications for depression and anxiety were built. In 1970, he was awarded the Nobel Prize in Physiology or Medicine.

Publications

Julius Axelrod Papers: <http://oculus.nlm.nih.gov/cgi/f/findaid/findaid-idx?c.nlmfindaid;idno=axelrod;view=reslist;idno=axelrod;sbview=standard;focusrgn=C02;cc.nlmfindaid;byte=4145043>; <http://profiles.nlm.nih.gov/ps/retrieve/Narrative/HH/p-nid/11>.

Ear, Nose, and Throat

2012: Understanding deafness: the role of auditory nerve mapping

Challenge

A key step in hearing development involves creating synaptic connections between the auditory nerve and sensory cells of the inner ear, yet how this happens is not fully understood. Further knowledge is needed to identify causes of hereditary hearing loss and eventually lead to effective treatments.

Advance

IRP researchers led by [Matthew Kelley, Ph.D.](#), demonstrated that expression of Pou3f4—a protein that helps transcribe DNA into RNA—interferes with auditory nerve axon growth by forcing the axons to grow along specific tracks toward inner ear sensory cells.

Impact

The finding helps explain why mutations in the Pou3f4 gene cause hearing loss. It may also lead to improvements in the function of cochlear implants, which must connect with the auditory nerve to alleviate deafness.

Publications

Coate TM, Raft S, Zhao X, Ryan AK, Crenshaw EB 3rd, Kelley MW. [Otic mesenchyme cells regulate spiral ganglion axon fasciculation through a Pou3f4/EphA4 signaling pathway](#). *Neuron*. 2012 Jan 12;73(1):49-63.

Endocrine System (Hormones)

2012: Taking a closer look at our on/off relationship with insulin

Challenge

Diabetes now affects more than 25 million people of all ages¹ yet the molecular underpinnings of the disease remain unclear. Although the overall pathways that drive the production of insulin are known, the molecular mechanisms that control rapid changes in insulin synthesis—for example following a meal—are not.

Advance

IRP investigators led by Eun Kyung Lee, Ph.D., identified a previously unknown component of the pathway—an RNA-binding protein named HuD, expressed in pancreatic β cells—that can bind insulin mRNA and inhibit its translation into protein, essentially blocking its production. The researchers also showed that, in response to increased glucose levels, HuD releases insulin mRNA, allowing the production of insulin protein.

Impact

The discovery that an RNA-binding protein can repress insulin translation in a rapidly reversible manner suggests that deficiencies in this protein could underlie some cases of diabetes. Work is underway to systematically compare HuD in the pancreatic β cells of diabetic and non-diabetic subjects, with the aim of determining if HuD could be a new therapeutic target.

Publications

Lee EK, Kim W, Tominaga K, Martindale JL, Yang X, Subaran SS, Carlson OD, Mercken EM, Kulkarni RN, Akamatsu W, Okano H, Perrone-Bizzozero NI, de Cabo R, Egan JM, Gorospe M. [RNA-binding protein HuD controls insulin translation](#). *Mol Cell*. 2012 Mar 30;45(6):826-35.

2011: Tracking the devastating effects of diethylstilbestrol (DES), a trans-placental carcinogen

Challenge

Between 1940 and the early 1970s, millions of pregnant women were given diethylstilbestrol (DES), the first synthetic estrogen, to prevent pregnancy complications. DES was later found to be a carcinogen that could cross the placenta and cause a range of health-related issues in women, including developmental defects and cancers. Rigorous follow-up reporting and analysis would be required to fully understand the devastating effects of DES on the women who were exposed in utero years before.

Advance

IRP investigators led by [Robert Hoover, M.D., Sc.D.](#), re-contacted more than 4,600 women who had participated in an initial landmark study, which described a rare vaginal cancer typically seen only in older women. These women were then followed long-term, and researchers were able to identify and track a number of adverse health outcomes linked to DES exposure, including pre-term delivery, ectopic pregnancy, and cancers of the cervix.

Impact

Without long-term follow-up studies, many outcomes of DES exposure might have gone unreported. This investigation, and others like it, serves as a model for an entire area of research focused on the role of endocrine disruption in early life and subsequent health effects.

Publications

Hoover RN, Hyer M, Pfeiffer RM, Adam E, Bond B, Cheville AL, Colton T, Hartge P, Hatch EE, Herbst AL, Karlan BY, Kaufman R, Noller KL, Palmer JR, Robboy SJ, Saal RC, Strohsnitter W, Titus-Ernstoff L, Troisi R. [Adverse health outcomes in women exposed in utero to diethylstilbestrol](#). *N Engl J Med*. 2011 6;365(14):1304-14.

Eyes and Vision

2011: Unraveling a complex world of neuronal connections

Challenge

Neurons have always appeared to be somewhat haphazardly wired together, yet their complex connectivity forms the basis of all neural circuits, whether in the brain, auditory tissues, or the retina of the eye, suggesting the process must have some degree of specificity.

Advance

IRP researchers led by [Kevin Briggman, Ph.D.](#), used new technologies, such as two-photon calcium imaging and serial block-face electron microscopy, to thoroughly visualize the neuronal circuitry used by the eye to detect motion.

Impact

The group's findings demonstrate that neuronal wiring in the retina is far more structured than initially thought, providing a basis for new neuronal models of development and disease, which could eventually lead to techniques for repairing damaged neuronal networks.

Publications

Briggman KL, Helmstaedter M, Denk W. [Wiring specificity in the direction-selectivity circuit of the retina](#). *Nature*. 2011 Mar 10;471(7337):183-8. doi: 10.1038/nature09818.

Immune System

2012: Discovering monogenic forms of common variable immunogenicity

Challenge

Common variable immunodeficiency (CVID) is one of the most common primary immunodeficiency diagnoses², but can take three to five years to be reached due to the non-specific nature of the symptoms. Early diagnosis of CVID is essential to ensuring reduced severity of infections via intravenous immunoglobulin (IVIG) treatment.

Advance

IRP researchers E. Michael Gertz, Ph.D., [Alejandro A. Schäffer, Ph.D.](#), and colleagues used genetic linkage analysis in families to identify homozygous mutations in the lipopolysaccharide responsive beige-like anchor gene (*LRBA*) as a frequent cause of CVID in patients who have early onset and autoimmune manifestations.

2 <http://www.aaaai.org/conditions-and-treatments/primary-immunodeficiency-disease/common-variable-immunodeficiency.aspx>

Impact

LRBA-deficient patients can now receive a prompt diagnosis via genetic analysis and start IVIG treatment sooner, which helps reduce the severity of recurrent infections and improves overall outcomes.

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Publications

Lopez-Herrera G, Tampella G, Pan-Hammarström Q, Herholz P, Trujillo-Vargas CM, Phadwal K, Simon AK, Moutschen M, Etzioni A, Mory A, Srugo I, Melamed D, Hultenby K, Liu C, Baronio M, Vitali M, Philippet P, Dideberg V, Aghamohammadi A, Rezaei N, Enright V, Du L, Salzer U, Eibel H, Pfeifer D, Veelken H, Stauss H, Lougaris V, Plebani A, Gertz EM, Schäffer AA, Hammarström L, Grimbacher B. [Deleterious Mutations in LRBA Are Associated with a Syndrome of Immune Deficiency and Autoimmunity](#). *Am J Hum Genet*. 2012 8;90(6):986–1001.

.....

2011: Reclassification of diseases improves understanding and outcomes

Challenge

Little is known about the causes or how to treat a group of rare heterogeneous autoimmune muscle diseases called idiopathic inflammatory myopathies, including Dermatomyositis, Polymyositis, and Inclusion Body Myositis. For unknown reasons, these diseases are increasing in prevalence in both children and adults, and a better understanding of their pathogenesis, underlying genetics, and molecular basis is urgently needed.

Advance

IRP researchers led by [Frederick W. Miller, M.D., Ph.D.](#), took a novel approach to understanding these heterogeneous syndromes and showed that the genetic and environmental risk factors, symptoms, and responses to therapy and prognosis can be predicted by categorizing the syndromes into mutually exclusive and stable phenotypes based on clinical and immune response features.

Impact

Redefining autoimmune muscle diseases into novel phenotypes has advanced the understanding of their unique pathogenesis and helped clinicians to recognize and manage these debilitating disorders.

.....

Publications

Rider LG, Miller FW. [Deciphering the clinical presentations, pathogenesis, and treatment of the idiopathic inflammatory myopathies](#). *JAMA*. 2011 Jan 12;305(2):183-90. doi: 10.1001/jama.2010.1977.

Miller FW. [New approaches to the assessment and treatment of the idiopathic inflammatory myopathies](#). *Ann Rheum Dis*. 2012 Apr;71 Suppl 2:i82-5.

.....

Kidney and Urinary System

2010: Understanding health disparities in kidney disease

Challenge

African Americans experience higher rates of kidney disease than do European-Americans, yet the increased prevalence of chronic kidney and end-stage kidney diseases in populations of African ancestry remains largely unexplained.

Advance

IRP researchers [Jeffrey Kopp, M.D.](#), and [Cheryl Winkler, Ph.D.](#), led a team that identified a genetic region on chromosome 22 within a specific gene—MYH9, a key component of the actin cytoskeleton—that genetically predisposes individuals to chronic kidney disease. Genetic variation in this region substantially explains the major health disparity between African Americans and those of non-African descent.

Impact

The finding inspired subsequent work on this locus, led by Dr. Martin Pollak, that identified the main contributor as genetic variants in APOL1, encoding apolipoprotein L1. APOL1 is a component of the innate immune system, and work defining how the variants disrupt cell function may offer new pharmacologic approaches to treating kidney disease.

Publications

Kopp JB, Smith MW, Nelson GW, Johnson RC, Freedman BI, Bowden DW, Oleksyk T, McKenzie LM, Ahuja TS, Berns JS, Cho ME, Dart RA, Kimmel PL, Korbet SM, Michel DM, Mokrzycki MH, Schelling JR, Simon E, Trachtman H, Vlahov D, Kajiyama H, Winkler CA. [MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis](#). *Nature Genet.* 2008 Oct;40(10):1175-84.

Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzuzeau P, Freedman BI, Bowden DW, Langfeld CD, Olesyk TK, Knob AU, Bernhardt AJ, Hicks PJ, Nelson GW, Vanhollebeke B, Winkler CW, Kopp JB, Pays E, Pollak MR. [Association of trypanolytic ApoL1 variants with kidney disease in African-Americans](#). *Science.* 2010 Aug 13;329(5993):841-5.

Kopp JB, Nelson GW, Sampath K, Johnson RC, Genovese G, An P, Friedman D, Briggs W, Dart R, Korbet A, Mokrzycki M, Kimmel PL, Limou S, Ahuja TS, Berns JS, Simon E, Smith MC, Trachtman H, Michel DM, Schelling JR, Vlahov D, Pollak M, Winkler CA. [APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy](#). *J Am Soc Nephrol.* 2011 Nov;22(11):2129-37.

Parsa A, Kao WHL, Xie D, Asator BC, Li M, Hsu C0y, Feldman HI, Parekh RS, Kusek JW, Greene TH, Find JC, Anderson AH, Choi MJ, WrightJT, Lash JP, Freedman BI, Ojo A, Winkler CA, Rasj DS, Kopp JB, He J, Jensvold NG, Tao K, Lipkowitz JS, Appel, LS. [APOL1 risk variants, race and progression of chronic kidney disease](#). for the African-American Study of Kidney Disease and Hypertension (AASK) and the Chronic Renal Insufficiency Cohort (CRIC) Study Investigators. *New Eng J Med.* 2013 Dec 5;369(23):2183-96.

Mental Health and Behavior

2013: Identifying an Alzheimer's disease risk gene

Challenge

Alzheimer's disease is a devastating, progressive brain disease that affects as many as 5.1 million Americans, and is the most common cause of dementia among older people³. How the disease process begins remains unknown, creating an urgent need to better understand Alzheimer's disease risks.

Advance

Two international teams of researchers, including IRP researchers led by [Andrew Singleton, Ph.D.](#), identified a unique variant in the TREM2 gene—a gene involved in inflammation and the immune response—as a significant risk factor for the development of late-onset Alzheimer's disease.

Impact

For many years the only genetic variant consistently associated with late onset Alzheimer's disease was in the ApoE4 gene. These are the first studies to identify the involvement of TREM2 in the Alzheimer's disease process. TREM2 plays a very specific role within the immune system, which suggests that perturbation of this system in some way may lead to the development of the disease. Discovering that pathway now provides targets for potential therapies.

Publications

Guerreiro R, Wojtas A, Bras J, Carrasquillo M, Rogaeva E, Majounie E, Cruchaga C, Sassi C, Kauwe JS, Younkin S, Hazrati L, Collinge J, Pocock J, Lashley T, Williams J, Lambert JC, Amouyel P, Goate A, Rademakers R, Morgan K, Powell J, St George-Hyslop P, Singleton A, Hardy J; Alzheimer Genetic Analysis Group. [TREM2 Variants in Alzheimer's Disease](#). *N Engl J Med*. 2013 Jan 10;368(2):117-27. doi: 10.1056/NEJMoa1211851. Epub 2012 Nov 14.

2012: Spur of the moment purchase? Blame your orbitofrontal cortex

Challenge

Scientists have long assumed that an area of the brain called the orbitofrontal cortex plays a role in decision-making. While the idea gained widespread acceptance in the scientific community, it was based on correlative evidence. New research was needed to determine exactly what role the region plays, and how that may affect our understanding of certain diseases, for example addiction disorders.

Advance

IRP researchers led by [Geoffrey Schoenbaum, M.D., Ph.D.](#), designed a series of experiments and discovered that the orbitofrontal cortex in fact does play a role in decision-making, but only in spur-of-the-moment, quick decisions and not decisions made previously or through habit. This finding was true for both decision-making and learning—in other words, if a decision is assumed and doesn't occur, that knowledge can be used to drive the process of learning.

Impact

This research fundamentally changed scientific understanding of the orbitofrontal cortex's role in normal behavior and how its alteration may contribute to behaviors seen in addiction disorders. Future work will characterize how drugs such as cocaine adversely affect this region of the brain, as well as identify pre-clinical approaches to restore function to damaged regions.

.....

Publications

Jones JL, Esber GR, McDannald MA, Gruber AJ, Hernandez A, Mirens A, Schoenbaum G. [Orbitofrontal cortex supports behavior and learning using inferred but not cached values](#). *Science*. 2012 Nov 16;338(6109):953-6.

.....

2011: Stimulating new ideas on caffeine action in the brain

Challenge

Caffeine is one of the oldest and most widely consumed cognitive stimulants on earth. Although it has pharmacological effects on many brain areas, its primary physiological site of action has not been established. Understanding how caffeine functions may provide clues to understanding sleep disorders, depression, and a range of conditions involving altered cognitive functioning.

Advance

IRP researchers led by [Serena Dudek, Ph.D.](#), discovered that caffeine, at levels similar to that consumed by humans, along with similar, more selective A1 adenosine receptor blockers, strongly enhanced synaptic responses in an area of the brain known as "hippocampal area CA2." The hippocampus is known for its role in learning and memory.

Impact

By discovering that this small region of the brain is the primary site of caffeine action, these studies highlight the CA2 region as a potential target for drug development to combat symptoms of fatigue due to sleep deprivation and depression, as well as sleep disturbances in neurodevelopmental disorders such as autism.

.....

Publications

Simons SB, Caruana DA, Zhao M, Dudek SM. [Caffeine-induced synaptic potentiation in hippocampal CA2 neurons](#). *Nat Neurosci*. 2011 Nov 20;15(1):23-5.

.....

2010: The need for speed: A new approach to treating depressive disorders

Challenge

Current therapies for depressive disorders take many weeks to work, during which time the symptoms of depression, including suicidal thinking, persist and can be fatal. Patients need better treatments that begin relieving symptoms immediately.

Advance

IRP researchers led by [Carlos A. Zarate, M.D.](#), took a novel approach to the problem and discovered that a single infusion of ketamine provides a fast, robust, and sustained antidepressant effect, including reduction of suicidal thoughts within minutes.

Impact

Having demonstrated unprecedented speed of symptom relief, ketamine and its analogs are now being tested in clinical trials around the world and, if approved for use, could become a new standard of care for treating people with depressive disorders.

Publications

DiazGranados N, Ibrahim LA, Brutsche NE, Ameli R, Henter ID, Luckenbaugh DA, Machado-Vieira R, Zarate CA Jr. [Rapid resolution of suicidal ideation after a single ketamine infusion in patients with treatment-resistant major depression](#). *J Clin Psychiatry*. 2010;71:1605-11.

2008: Could you become addicted to something? Your genes reveal all

Challenge

Genetic influences on quitting smoking and beginning use of common addictive substances are well documented in the scientific literature. Doctors recommend prevention interventions for individuals who may be at risk of substance abuse. However, a test is needed to indicate the most urgent candidates for prevention intervention.

Advance

IRP researchers at the [National Institute on Drug Abuse \(NIDA\)](#) developed the first genetic test for smoking cessation and discovered that the test's score is able to robustly separate individuals who rapidly accelerate use of addictive substances from those who do not.

Impact

This is the first test to identify individuals at risk for addiction, who might benefit most from prevention efforts since they are more likely to escalate use if they start and have more difficulty quitting if they develop regular use, abuse, and dependence.

Publications

Uhl GR, Liu QR, Drgon T, Johnson C, Walther D, Rose JE, David SP, Niaura R, Lerman C. [Molecular genetics of successful smoking cessation: convergent genome-wide association study results](#). *Arch Gen Psychiatry*. 2008 Jun;65(6):683-93.

Drgon T, Montoya I, Johnson C, Liu QR, Walther D, Hamer D, Uhl GR. [Genome-wide association for nicotine dependence and smoking cessation success in NIH research volunteers](#). *Mol Med*. 2009 Jan-Feb;15(1-2):21-7.

1970: A sense of calm in bipolar disorder: The clinical trials of lithium

Challenge

In 1949, the Australian physician John Cade published a paper on using lithium salts to treat psychotic mania, noting that the drug produced a "pronounced calming effect"⁴. The publication piqued great interest among the psychiatry community, but large multicenter clinical studies were needed to confirm lithium's role as a potential new tool in the treatment of mania associated with bipolar disorder.

Advance

In the decades following Cade's publication, the [National Institute of Mental Health \(NIMH\)](#) and several university centers established large, rigorously controlled, multicenter clinical trials that clearly demonstrated the antimanic effects of lithium. The ability to convene, lead, and analyze data from these trials contributed to the FDA's 1970 approval of lithium to treat acute mania.

Impact

More than 60 years after its discovery, lithium is still the first-line therapy for treatment of bipolar disorder. In addition to being tremendously successful in treating the illness, lithium provides enormous financial savings by reducing the lost productivity of affected earners, homemakers, caregivers, and other individuals by billions of dollars annually⁵.

Publications

1970 Eskalith Approval: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=SearchDrugDetails>.

Skin, Hair, and Nails

2012: Only skin deep? New insights on retinoic acid in skin development

Challenge

Skin protects us from foreign organisms and allergens, but how it develops into a protective barrier is still unknown. Molecular-level understanding of the process could lead to treatments for skin conditions and diseases.

Advance

IRP scientists led by [Maria Morasso, Ph.D.](#), discovered that high levels of retinoic acid—a popular skin cream ingredient—during embryonic development in mouse models resulted in abnormalities of the epidermis, the outermost skin layer, and interfered with the skin's normal barrier function.

Impact

The new insights into abnormal skin development open a door that may lead to treatments for aberrant skin growth and barrier dysfunction associated with conditions ranging from hypothermia and prenatal dehydration to atopic dermatitis.

Publications

Okano J, Lichti U, Mamiya S, Aronova M, Zhang G, Yuspa S.H, Hamada H, Sakai Y and Morasso MI. [Increased retinoic acid levels through ablation of Cyp26b1 determine the processes of embryonic skin barrier formation and peridermal development.](#) *J Cell Sci.* 2012 Feb 24. [Epub ahead of print].



health & wellness

Environmental Health

1992/2012: Linking heavy exposure to diesel exhaust to lung cancer deaths in miners

Challenge

Despite numerous studies investigating the relationship between diesel engine exhaust exposure and risk of death from lung cancer, the lack of quantitative exposure data and large sample sizes restricted our ability to accurately evaluate this risk. Accurate evaluation of the exposure-response for diesel exhaust and lung cancer is critical for the millions of people around the world who are occupationally exposed to potentially fatal carcinogens.

Advance

In 1992, IRP researchers led by [Debra T. Silverman, Sc.D.](#), and colleagues at the [National Institute for Occupational Safety and Health \(NIOSH\)](#) embarked on a 20-year study of more than 12,000 miners, which became the first to show a statistically significant association between heavy exposure to diesel exhaust and lung cancer death.

Impact

These findings are important for public health, with implications for not only the 1.4 million American workers who are exposed to diesel exhaust in the workplace⁶, but also the many millions of urban populations in the U.S. and around the world who may be exposed to diesel exhaust.

Publications

Silverman DT, Samanic CM, Lubin JH, Blair AE, Stewart PA, Vermeulen R, Coble JB, Rothman N, Schleiff PL, Travis WD, Ziegler RG, Wacholder S, Attfield MD. [The Diesel Exhaust in Miners study: a nested case-control study of lung cancer and diesel exhaust.](#) *J Natl Cancer Inst.* 2012 6;104(11):855-68.

1957: Fluoridation: A public health milestone to make us all smile

Challenge

More than half a century ago, tooth loss and decay was a serious public health issue afflicting most people, often at a young age. Periodontal diseases and dental caries left 17 million Americans age 45 and older (about three in 10) with none of their natural teeth⁷. If researchers could discover a way to prevent tooth decay, everyone would benefit.

Advance

IRP investigators at the National Institute of Dental Research (now the [National Institute of Dental and Craniofacial Research \(NIDCR\)](#)) spearheaded studies in the 1940s and 1950s that showed the rate of tooth decay in children who drank fluoridated water fell more than 60 percent.

Impact

Water fluoridation stands out as one of the most significant and cost-effective public health milestones of the last century.

Publications

Francis A. Arnold, Jr. [Grand Rapids Fluoridation Study—Results Pertaining to the Eleventh Year of Fluoridation](#). *Am J Public Health Nations Health*. 1957 May;47(5):539–545.

The Story of Fluoridation - <http://www.nidcr.nih.gov/oralhealth/topics/fluoride/thestoryoffluoridation.htm>.

Food, Nutrition, and Metabolism

2013: The calculus of calories: mathematical models to quantify obesity and its treatment

Challenge

Obesity presents a major public health challenge. Many obesity interventions have been proposed to help both individuals and populations, but previous methods for predicting weight loss did not account for dynamic changes in metabolism and body composition as people gain and lose weight.

Advance

IRP researchers led by [Kevin D. Hall, Ph.D.](#), and [Carson C. Chow, Ph.D.](#), created and validated novel mathematical models of human metabolism and body weight dynamics to provide accurate predictions about the development of obesity and its treatment in adults and children.

Impact

Award-winning Web and smartphone applications for predicting human weight dynamics based on the new algorithms have been used by more than one million people so far. The models quantify the calorie imbalance underlying the obesity epidemic and predict how interventions will impact body weight in individuals, as well as in entire populations.

Publications

Hall KD, Butte NF, Swinburn BA, Chow CC. [Dynamics of childhood growth and obesity: development and validation of a quantitative mathematical model](#). *Lancet Diabetes Endocrinol*. 2013 Oct 1;1(2):97-105

Lin BH, Smith TA, Lee JY, Hall KD. [Measuring weight outcomes for obesity intervention strategies: The case of a sugar-sweetened beverage tax](#). *Econ Hum Biol*. 2011 Dec;9(4):329-41.

Hall KD, Sacks G, Chandramohan D, Chow CC, Wang YC, Gortmaker S, Swinburn BA. [Quantification of the effect of energy imbalance on bodyweight](#). *The Lancet*. 2011 Aug 27;378(9793):826-37

Hall KD, Guo J, Dore M, Chow CC. [The progressive increase of food waste in America and its environmental impact](#). *PLoS One*. 2009 Nov 25;4(11):e7940.

Substance Abuse

2014: Approaching a treatment for marijuana addiction

Challenge

The number of past-month marijuana users in the U.S. in 2012 was approximately 18 million, compared to 1.6 million cocaine and 0.3 million heroin users. Although estimates from research show that dependence rates for marijuana are lower than for cocaine or heroin (9 percent versus 17 and 23 percent, respectively), higher marijuana usage means that marijuana dependence is more prevalent than dependence on cocaine or heroin. Despite a clear need, there are currently no FDA-approved medications to treat marijuana addiction.

Advance

IRP researchers led by Zuzana Justinova, M.D., Ph.D., and [Steven R. Goldberg, Ph.D.](#), discovered that enhancing levels of kynurenic acid in two reward-related brain areas, the nucleus accumbens (NAc) and the ventral tegmental area (VTA), of an animal model significantly reduced the neurochemical and behavioral effects of delta-9-tetrahydrocannabinol (THC), the main psychoactive ingredient in cannabis.

Impact

The team's finding suggests that modulation of kynurenic acid levels could be a pharmacological strategy for achieving abstinence from cannabis and preventing relapse.

Publications

Justinova Z, Mascia P, Wu HQ, Secci ME, Redhi GH, Panlilio LV, Scherma M, Barnes C, Parashos A, Zara T, Fratta W, Solinas M, Pistis M, Bergman J, Kangas BD, Ferré S, Tanda G, Schwarcz R, Goldberg SR. [Reducing cannabinoid abuse and preventing relapse by enhancing endogenous brain levels of kynurenic acid](#). *Nat Neurosci*. 2013 Nov;16(11):1652-61.

2012: A non-addictive form of cocaine? A potential therapy awaits

Challenge

Cocaine addiction is a chronic and relapsing disorder that affects millions worldwide⁸, exerting a toll in lives lost, families torn, and communities destroyed. No medications are currently available to treat cocaine addiction.

Advance

IRP and international researchers led by [Amy Hauck Newman, Ph.D.](#), discovered that R-modafinil, like cocaine, inhibits dopamine uptake, but binds to the dopamine transporter in a unique fashion that may not result in the same addictive response as cocaine.

Impact

Molecular and preclinical pharmacological findings support translation of R-modafinil studies to clinical trials in the cocaine-abusing population as a potential treatment.

Publications

Loland CJ, Mereu M, Okunola OM, Cao J, Prisinzano TE, Mazier S, Kopajtic T, Shi L, Katz JL, Tanda G, Newman AH. [R-modafinil \(armodafinil\): a unique dopamine uptake inhibitor and potential medication for psychostimulant abuse](#). *Biol Psychiatry*. 2012 Sep 1;72(5):405-13.

2012: Chronic drinking may alter the brain and increase PTSD risk

Challenge

While alcoholism and anxiety disorders like post-traumatic stress disorder (PTSD) are often seen together, few studies have explored how chronic alcohol exposure can affect recovery from a traumatic experience.

Advance

[Andrew Holmes, Ph.D.](#), and colleagues used an animal model to determine that chronic alcohol exposure remodels the brain's neuronal wiring, impairing the ability to suppress fear and recover normally from a traumatic experience.

Impact

The results show that chronic drinking rewires brain circuitry, which may increase susceptibility for anxiety disorders like PTSD. These findings provide a basis for the development of neurochemical therapies that target these specific areas of the brain with an aim to restoring normal functions.

Publications

Holmes A, Fitzgerald PJ, MacPherson KP, DeBrouse L, Colacicco G, Flynn SM, Masneuf S, Pleil KE, Li C, Marcinkiewicz CA, Kash TL, Gunduz-Cinar O, Camp M. [Chronic alcohol remodels prefrontal neurons and disrupts NMDAR-mediated fear extinction encoding](#). *Nat Neurosci*. 2012 Oct;15(10):1359-61.



conditions & diseases

Cancers

2010: Deciphering how chromosomal mix-ups lead to tumors

Challenge

Scientists do not fully understand the underlying genetic causes of lymphoma and leukemia. If they can identify the location and cause of errors in the genome, that knowledge could provide new therapeutic targets for treatment of disease.

Advance

IRP scientists led by [Rafael Casellas, Ph.D.](#), discovered that recurrent chromosomal rearrangements, or translocations, occur when broken strands of DNA from one chromosome are mistakenly joined with those of another, which can lead to uncontrolled cell growth or cancer. The researchers found that an enzyme called Activation Induced Deaminase (AID) plays a key role in promoting translocations.

Impact

The new findings helped clarify the origin of cancer-inducing translocations and identified AID as a potential therapeutic target to prevent the development of many human cancers.

Publications

Klein IA, Resch W, Jankovic M, Oliveira T, Yamane A, Nakahashi H, Di Virgilio M, Bothmer A, Nussenzweig A, Robbiani DF, Casellas R, Nussenzweig MC. Pavri R, Gazumyan A, Jankovic M, Di Virgilio M, Klein I, Ansarah-Sobrinho C, Resch W, Yamane A, Reina San-Martin B, Barreto V, Nieland TJ, Root DE, Casellas R, Nussenzweig MC. [Translocation-capture sequencing reveals the extent and nature of chromosomal rearrangements in B lymphocytes](#). *Cell*. 2011 Sep 30;147(1):95-106.

2001(+): The HPV vaccine: Two decades of research pays off

Challenge

Human papillomavirus (HPV) is the most common sexually-transmitted infection around the world⁹. With more than 40 variations and clear linkages to cervical cancer and a range of genital cancers¹⁰, the challenge to develop a broadly protective vaccine was unparalleled.

Advance

Douglas R. Lowy, M.D., and John T. Schiller, Ph.D., spent more than two decades investigating how to prevent HPV infection, culminating in the discovery and production of virus-like particles (VLPs), which block certain mechanisms essential to HPV infection. Their work led to the production of the first commercially available vaccine against the two deadliest forms of the virus, HPV16 and HPV18, in 2006.

Impact

The HPV vaccine has been shown to be 100 percent effective, and governments across the globe now recommend routine vaccination of all girls (and in some countries, boys) aged 11 or 12 years. The hope is that widespread vaccination could reduce HPV-associated cancer deaths by up to two-thirds¹¹.

Publications

Harro CD, Pang YY, Roden RB, Hildesheim A, Wang Z, Reynolds MJ, Mast TC, Robinson R, Murphy BR, Karron RA, Dillner J, Schiller JT, Lowy DR. [Safety and immunogenicity trial in adult volunteers of a human papillomavirus 16 L1 virus-like particle vaccine](#). *J Natl Cancer Inst*. 2001;93:284-292.

FDA Licenses New Vaccine for Prevention of Cervical Cancer and Other Diseases in Females Caused by Human Papillomavirus *Rapid Approval Marks Major Advancement in Public Health*: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108666.htm>.

2001(+): There's no “magic bullet” for cancer. Or is there?

Challenge

In the U.S., it is expected that approximately 1.5 million people will be diagnosed with cancer each year, and one third of those will die of the disease¹². To combat such a complex and multifactorial disease, doctors need more efficient and targeted treatments to destroy cancer cells without harming healthy tissues.

Advance

Ira Pastan, M.D., and colleagues created recombinant immunotoxins that specifically target cancer cells. The “magic bullets” are made by genetically engineering a potent bacterial toxin, *Pseudomonas exotoxin A*, with an antibody fragment that selectively binds to receptors on the cancer cell surface.

Impact

Delivering a toxic payload to the inside of a cancer cell while leaving healthy tissue unscathed is a major step forward in the battle against cancer. Research continues to determine which tumors might respond best to this type of targeted approach, but clinical trials are already underway, with some immunotoxins producing partial or complete remissions.

Publications

Onda M, Olafsen T, Tsutsumi Y, Bruland ØS, Pastan I. [Cytotoxicity of Antiosteosarcoma Recombinant Immunotoxins Composed of TP-3 Fv Fragments and a Truncated Pseudomonas Exotoxin A](#). *J Immunother* 1991. 2001 Mar;24(2):144-150.

Kreitman RJ, Tallman MS, Robak T, Coutre S, Wilson WH, Stetler-Stevenson M, Fitzgerald DJ, Lechleider R, Pastan I. [Phase I trial of anti-CD22 recombinant immunotoxin moxetumomab pasudotox \(CAT-8015 or HA22\) in patients with hairy cell leukemia](#). *J Clin Oncol*. 2012 May 20;30(15):1822-8.

11 <http://www.cancer.gov/cancertopics/factsheet/prevention/HPV-vaccine>

12 <http://seer.cancer.gov/statfacts/html/all.html>

2000(+): Finding one disease is actually many: Diffuse large B-cell lymphomas

Challenge

Some patients with diffuse large B-cell lymphomas (DLBCL) live longer and respond better to therapy than others, highlighting an urgent need to better understand the disease's underlying biology and inform more effective treatment approaches.

Advance

IRP researchers led by [Louis Staudt, M.D., Ph.D.](#), profiled the genes expressed in patients with DLBCL and found important differences, leading to the identification of three new molecularly and clinically distinct subclasses of the disease: germinal center B-cell-like, activated B-cell-like (ABC), and primary mediastinal B-cell lymphoma (PMBL).

Impact

These discoveries revealed new molecular targets based on each subclass and informed the development of new therapies. For example, the discovery that one subgroup of DLBCL relies on the NF- κ B signaling pathway allowed physicians to target that pathway directly, leading to complete remission in a number of cases.

Publications

Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, Boldrick JC, Sabet H, Tran T, Yu X, Powell JI, Yang L, Marti GE, Moore T, Hudson J Jr, Lu L, Lewis DB, Tibshirani R, Sherlock G, Chan WC, Greiner TC, Weisenburger DD, Armitage JO, Warnke R, Levy R, Wilson W, Grever MR, Byrd JC, Botstein D, Brown PO, Staudt LM. [Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling](#). *Nature*. 2000 Feb 3;403(6769).

Wright G, Tan B, Rosenwald A, Hurt EH, Wiestner A, Staudt LM. [A gene expression-based method to diagnose clinically distinct subgroups of diffuse large B cell lymphoma](#). *Proc Natl Acad Sci U S A*. 2003 Aug 19;100(17):9991-6.

1995: Lifting the lid on kidney cancer: Exposing the underlying genetics

Challenge

In the early 1980s, little was known about the genetic basis of kidney cancer, and patients continued to succumb to the disease despite chemotherapy treatment. Today, more than 13,000 renal carcinoma patients in the U.S. still die every year¹³, demonstrating a continuing need for better approaches to battling this disease

Advance

During the past two decades, [W. Marston Linehan, M.D.](#), and colleagues made seminal discoveries about the genetic basis of kidney cancer, including identification of the von Hippel-Lindau (VHL) gene (the 6th human cancer gene identified) and the hereditary papillary renal cell carcinoma (HPRC), hereditary leiomyomatosis, and renal cell cancer (HLRCC) genes: *c-Met*, *BHD*, and *fumarate hydratase*.

Impact

These discoveries have led to new approaches for molecular-based therapies against renal carcinoma, and clinical trials are now ongoing with a number of promising treatments.

Publications

Linehan WM, Lerman MI, Zbar B. [Identification of the von Hippel-Lindau \(VHL\) gene. Its role in renal cancer.](#) *JAMA*. 1995 Feb 15;273(7):564-70.

Schmidt L, Duh FM, Chen F, Kishida T, Glenn G, Choyke P, Scherer SW, Zhuang Z, Lubensky I, Dean M, Allikmets R, Chidambaram A, Bergerheim UR, Feltis JT, Casadevall C, Zamarron A, Bernues M, Richard S, Lips CJ, Walther MM, Tsui LC, Geil L, Orcutt ML, Stackhouse T, Lipan J, Slife L, Brauch H, Decker J, Niehans G, Hughson MD, Moch H, Storkel S, Lerman MI, Linehan WM, Zbar B. [Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas.](#) *Nat Genet*. 1997 May;16(1):68-73.

Toro JR, Nickerson ML, Wei MH, Warren MB, Glenn GM, Turner ML, Stewart L, Duray P, Tourre O, Sharma N, Choyke P, Stratton P, Merino M, Walther MM, Linehan WM, Schmidt LS, Zbar B. [Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in North America.](#) *Am J Hum Genet*. 2003 Jul;73(1):95-106.

1989(+): Discovering a growth factor and its incredible healing powers

Challenge

For decades, nothing was available to prevent or reduce the severity of oral mucositis (ulcerative lesions of the mouth), a common side effect of high doses of chemotherapy and radiation, which increases the risk of infection in cancer patients. A therapy was needed to reduce the incidence of this painful and life-threatening side-effect of many cancer therapies.

Advance

In the late 1980s, IRP scientists [Jeffrey Rubin, M.D., Ph.D.](#), Paul Finch, Ph.D., and [Stuart A. Aaronson, M.D.](#), discovered and purified keratinocyte growth factor (KGF). Several studies later demonstrated that KGF occurs naturally and stimulates the growth of surface layer cells in the mouth, which speeds healing of ulcers, reducing infection risks. The NIH partnered with Amgen in 1992 to develop Kepivance, a therapeutic treatment based on KGF.

Impact

Clinical trial results showed that Kepivance decreased the incidence and duration of severe oral mucositis in cancer patients who were given intensive chemotherapy and radiation prior to bone marrow/blood cell transplants. FDA approved in 2004, Kepivance now benefits about 11,000 American adults who undergo bone marrow transplants each year¹⁴.

Publications

Rubin JS, Osada H, Finch PW, Taylor WG, Rudikoff S, Aaronson SA. [Purification and characterization of a newly identified growth factor specific for epithelial cells.](#) *Proc Natl Acad Sci U S A*. 1989 Feb;86(3):802-6.

Kepivance FDA Approval Package: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/125103s000_KepivanceTOC.cfm.

Genetics and Birth Defects

2013: Power in numbers: identifying new genes associated with ankylosing spondylitis

Challenge

Ankylosing spondylitis is an incurable inflammatory arthritis of the spine that most often begins in young adulthood and can lead to life-long inflexibility, posture changes, and pain. Researchers have explored the disease’s genetic risk factors for decades, but further knowledge is necessary to understand what causes the inflammation and how to treat it.

Advance

IRP researchers led by [Michael M. Ward, M.D.](#), partnered with the International Genetics of Ankylosing Spondylitis Consortium to compare genes from thousands of people with ankylosing spondylitis to those from people without the disease. The team discovered 13 new genetic markers associated with ankylosing spondylitis and confirmed the importance of 12 previously identified biomarkers.

Impact

Results from this study help researchers pinpoint therapeutic targets—such as the interleukin-23 inflammation pathway and the immune system protein HLA-B27—that may lead to effective treatments for controlling ankylosing spondylitis.

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Publications

International Genetics of Ankylosing Spondylitis Consortium (IGAS); Cortes A, Hadler J, Pointon JP, Robinson PC, Karaderi T, Leo P, Cremin K, Pryce K, Harris J, Lee S, Joo KB, Shim SC, Weisman M, Ward M, Zhou X, Garchon HJ, Chiocchia G, Nossent J, Lie BA, Førre O, Tuomilehto J, Laiho K, Jiang L, Liu Y, Wu X, Bradbury LA, Elewaut D, Burgos-Vargas R, Stebbings S, Appleton L, Farrah C, Lau J, Kenna TJ, Haroon N, Ferreira MA, Yang J, Mulero J, Fernandez-Sueiro JL, Gonzalez-Gay MA, Lopez-Larrea C, Deloukas P, Donnelly P; Australo-Anglo-American Spondyloarthritis Consortium (TASC); Groupe Française d’Etude Génétique des Spondylarthrites (GFECS); Nord-Trøndelag Health Study (HUNT); Spondyloarthritis Research Consortium of Canada (SPARCC); Wellcome Trust Case Control Consortium 2 (WTCCC2), Bowness P, Gafney K, Gaston H, Gladman DD, Rahman P, Maksymowych WP, Xu H, Crusius JB, van der Horst-Bruinsma IE, Chou CT, Valle-Oñate R, Romero-Sánchez C, Hansen IM, Pimentel-Santos FM, Inman RD, Vider V, Martin J, Breban M, Reveille JD, Evans DM, Kim TH, Wordsworth BP, Brown MA. [Identification of multiple risk variants for ankylosing spondylitis through high-density genotyping of immune-related loci.](#) *Nat Genet.* 2013 Jun 9;45(7):730-8.

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2013: Tackling the mysteries of osteosarcoma in children by uncovering gene variants associated with risk

Challenge

Osteosarcoma is the most common malignant bone tumor in children and adolescents. However, researchers know very little about its common genetic risk factors, partly due to the tumor’s rarity in the general population: there are approximately 800 new cases in the United States each year.

Advance

IRP investigators lead by [Sharon Savage, M.D.](#), completed the first genome-wide association study of genetic risk variants for osteosarcoma. The researchers discovered that osteosarcoma patients with specific variants in different genetic loci—within the glutamate receptor metabotropic 4 (GRM4) gene and on chromosome 2p25.2—were at significantly increased risk of osteosarcoma.

Impact

If validated in other populations, the identified genetic markers could serve as a tool that helps researchers find new mechanisms of osteosarcoma development and possibly help clinicians diagnose individuals at risk of osteosarcoma. In addition, IRP researchers are leading analyses to uncover genetic factors associated with osteosarcoma clinical outcomes, such as metastasis or response to therapy.

Publications

Savage SA, Mirabello L, Wang Z, Gastier-Foster JM, Gorlick R, Khanna C, Flanagan AM, Tirabosco R, Andrulis IL, Wunder JS, Gokgoz N, Patiño-García A, Sierrasesúmaga L, Lecanda F, Kurucu N, İlhan IE, Sari N, Serra M, Hattinger C, Picci P, Spector LG, Barkauskas DA, Marina N, de Toledo SR, Petrilli AS, Amary MF, Halai D, Thomas DM, Douglass C, Meltzer PS, Jacobs K, Chung CC, Berndt SI, Purdue MP, Caporaso NE, Tucker M, Rothman N, Landi MT, Silverman DT, Kraft P, Hunter DJ, Malats N, Kogevinas M, Wacholder S, Troisi R, Helman L, Fraumeni JF Jr, Yeager M, Hoover RN, Chanock SJ. [Genome-wide association study identifies two susceptibility loci for osteosarcoma](#). *Nat Genet.* 2013 Jul;45(7):799-803.

2012: A new approach to treating organ damage in inflammatory diseases

Challenge

The rare and debilitating genetic disorder known as neonatal-onset multisystem inflammatory disease (NOMID) causes persistent inflammation and ongoing tissue damage, often beginning within the first weeks of life. Because NOMID affects numerous organs and body systems, early diagnosis and treatment are important for preventing long-term organ damage.

Advance

IRP researchers led by [Raphaela Goldbach-Mansky, M.D., M.H.S.](#), discovered that blocking interleukin-1 (IL-1)—an inflammatory protein made by immune system cells—with increasing doses of the FDA-approved rheumatoid arthritis treatment, anakinra, could preserve organ function in most patients.

Impact

Although overproduction of IL-1 can lead to damaging inflammation, the immune system still requires certain levels of IL-1 to help fight infections. The results alleviate concern that treating NOMID by blocking IL-1 may leave the body vulnerable to infection by showing that anakinra is effective and well-tolerated in the treatment of NOMID.

Publications

Sibley CH, Plass N, Snow J, Wiggs EA, Brewer CC, King KA, Zalewski C, Kim HJ, Bishop R, Hill S, Paul SM, Kicker P, Phillips Z, Dolan JG, Widemann B, Jayaprakash N, Pucino F, Stone DL, Chapelle D, Snyder C, Butman JA, Wesley R, Goldbach-Mansky R. [Sustained response and prevention of damage progression in patients with neonatal-onset multisystem inflammatory disease treated with anakinra: a cohort study to determine three- and five-year outcomes](#). *Arthritis Rheum.* 2012 Jul;64(7):2375-86.

2012: DNA and damage control: A complex web of players

Challenge

Fanconi anemia (FA) is a genetic disease characterized by congenital defects, bone marrow failure, and cancer susceptibility. At least 15 genes are known to be involved in the disease¹⁵, whose gene products normally constitute a DNA damage response network that is essential for repair of DNA strand damage. Understanding how FA proteins are recruited to the DNA damage sites could uncover new drug targets.

Advance

IRP investigators led by Zhijiang Yan, Ph.D., showed for the first time that the FA network is controlled by a novel ubiquitin signaling cascade initiated by the RNF8 ubiquitin ligase and its partner, UBC13, and mediated by FAAP20, a newly described component of the FA core complex.

Impact

Transmission of DNA damage signals is vital in setting the rate and extent of DNA repair during aging and the development of cancer. The newly discovered cascade is now a potential target for drug intervention: agonists that promote repair could aid in the function of aging cells, whereas antagonists that inhibit the cascade could disrupt DNA repair in cancer cells to make them more susceptible to chemotherapy.

Publications

Yan Z, Guo R, Paramasivam M, Shen W, Ling C, Fox D 3rd, Wang Y, Oostra AB, Kuehl J, Lee DY, Takata M, Hoatlin ME, Schindler D, Joenje H, de Winter JP, Li L, Seidman MM, Wang W. [A ubiquitin-binding protein, FAAP20, links RNF8-mediated ubiquitination to the Fanconi anemia DNA repair network.](#) *Mol Cell*. 2012 Jul 13;47(1):61-75.

2011: Team science unravels the link between ALS and FTD

Challenge

Amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) is a fatal neurodegenerative disorder that leads to progressive paralysis and respiratory failure¹⁶. Frontotemporal dementia (FTD) is the most common form of dementia in the under-65 population¹⁷. Researchers have long suspected an overlap between the two diseases, but the molecular and genetic basis of this intersection was unknown.

Advance

[Bryan J. Traynor, M.D., Ph.D.](#), brought historically competitive research groups together to focus their efforts on identifying the underlying genetic cause of ALS and FTD. The new international consortium discovered that an insertion mutation disrupting the *C9ORF72* gene is the most common genetic cause of both ALS and FTD identified to date, accounting for 40 percent of all familial cases of ALS and FTD in European and North American populations.

Impact

Discovery of this mutation changed scientific understanding of neurodegenerative diseases, influencing the diagnosis and investigation of ALS and FTD and, for the first time, mechanistically linking the two disorders. It also suggested a therapeutic target for gene therapy, with further research ongoing.

15 <http://ghr.nlm.nih.gov/condition/fanconi-anemia>

16 http://www.ninds.nih.gov/disorders/amyotrophiclateralsclerosis/detail_ALS.htm

17 <http://www.aafp.org/afp/2010/1201/p1372.html>

Publications

Renton AE, Majounie E, Waite A, Simón-Sánchez J, Rollinson S, Gibbs JR, Schymick JC, Laaksovirta H, van Swieten JC, Myllykangas L, Kalimo H, Paetau A, Abramzon Y, Remes AM, Kaganovich A, Scholz SW, Duckworth J, Ding J, Harmer DW, Hernandez DG, Johnson JO, Mok K, Ryten M, Trabzuni D, Guerreiro RJ, Orrell RW, Neal J, Murray A, Pearson J, Jansen IE, Sondervan D, Seelaar H, Blake D, Young K, Halliwell N, Callister JB, Toulson G, Richardson A, Gerhard A, Snowden J, Mann D, Neary D, Nalls MA, Peuralinna T, Jansson L, Isoviita VM, Kaivorinne AL, Hölttä-Vuori M, Ikonen E, Sulkava R, Benatar M, Wu J, Chiò A, Restagno G, Borghero G, Sabatelli M; ITALSGEN Consortium, Heckerman D, Rogaeva E, Zinman L, Rothstein JD, Sendtner M, Drepper C, Eichler EE, Alkan C, Abdullaev Z, Pack SD, Dutra A, Pak E, Hardy J, Singleton A, Williams NM, Heutink P, Pickering-Brown S, Morris HR, Tienari PJ, Traynor BJ. [A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD.](#) *Neuron*. 2011 Oct 20;72(2):257-68.

2010-2012: Using genetics to understand stuttering

Challenge

Stuttering is a common but poorly understood speech disorder. Current therapy options show only limited long-term success for individuals who stutter beyond childhood.

Advance

Recognizing that stuttering often runs in families, IRP researchers led by [Dennis Drayna, Ph.D.](#), sought to understand the disorder's hereditary basis. The team identified a number of mutations in three genes that control the production of enzymes involved in cellular waste disposal via the lysosome. When these enzymes are disrupted, bone, connective tissue, and neurologic symptoms typically follow.

Impact

The discovery that stuttering may have a genetic component related to the lysosome has spurred further research towards understanding how dysregulation of this biochemical pathway could give rise to stuttering and what pharmacotherapeutic options may be effective in treatment.

Publications

Raza MH, Amjad R, Riazuddin S, Drayna D. [Studies in a consanguineous family reveal a novel locus for stuttering on chromosome 16q.](#) *Hum Genet*. 2012 Feb;131(2):311-3.

Raza MH, Riazuddin S, Drayna D. [Identification of an autosomal recessive stuttering locus on chromosome 3q13.2-3q13.33.](#) *Hum Genet*. 2010 Oct;128(4):461-3.

Kang C, Riazuddin S, Mundorff J, Krasnewich D, Friedman P, Mullikin JC, Drayna D. [Mutations in the lysosomal enzyme-targeting pathway and persistent stuttering.](#) *N Engl J Med*. 2010 Feb 25;362(8):677-85.

1997(+): Breaking down complex autoinflammatory diseases, and building up new hope

Challenge

In some individuals, the immune system attacks the body's own tissues, causing inflammation. The recent discovery that a subset of autoinflammatory diseases has genetic components complicates diagnosis, making development of therapeutics a challenge.

Advance

Daniel L. Kastner, M.D., Ph.D., and colleagues have identified, classified, and characterized more than 10 new hereditary autoinflammatory disease pathways, including FMF, TRAPS, NOMID, and DIRA. IRP scientists develop and test new therapies aimed at reducing inflammation in these diseases, in some cases completely reversing them.

Impact

Patients with complex genetic autoinflammatory disorders may soon no longer need to experience trial and error prescribing in an effort to control their debilitating symptoms. For some diseases, genetic analyses combined with molecular studies of the affected pathways can inform the selection of targeted therapeutics and provide immediate and sustained relief.

Publications

International FMF Consortium (Kastner DL, corresponding author). [Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever](#). *Cell*. 1997;90:797-807.

McDermott MF, Aksentijevich I, Galon J, McDermott EM, Ogunkolade BW, Centola M, Mansfield E, Gadina M, Karenko L, Pettersson T, McCarthy J, Frucht DM, Aringer M, Torosyan Y, Teppo AM, Wilson M, Karaarslan HM, Wan Y, Todd I, Wood G, Schlimgen R, Kumarajeewa TR, Cooper SM, Vella JP, Amos CI, Mulley J, Quane KA, Molloy MG, Ranki A, Powell RJ, Hitman GA, O'Shea JJ, Kastner DL. [Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes](#). *Cell*. 1999;97:133-144.

Aksentijevich I, Nowak M, Mallah M, Chae JJ, Watford WT, Hofmann SR, Stein L, Russo R, Goldsmith D, Dent P, Rosenberg HF, Austin F, Remmers EF, Balow JE Jr, Rosenzweig S, Komarow H, Shoham NG, Wood G, Jones J, Mangra N, Carrero H, Adams BS, Moore TL, Schikler K, Hoffman H, Lovell DJ, Lipnick R, Barron K, O'Shea JJ, Kastner DL, Goldbach-Mansky R. [De novo CIAS1 mutations, cytokine activation, and evidence for genetic heterogeneity in patients with neonatal-onset multisystem inflammatory disease \(NOMID\): a new member of the expanding family of pyrin-associated autoinflammatory diseases](#). *Arthritis Rheum*. 2002;46:3340-3348.

1991: Therapy for inherited enzyme deficiencies

Challenge

Gaucher disease stems from deficiency of the enzyme glucocerebrosidase, leading to accumulated lipids that cause symptoms ranging from mild pigmentation to life-threatening seizures and brain damage. Although the concept of enzyme replacement had been proposed many years ago, a targeted approach is needed to ensure delivery of the enzyme to the correct cell type.

Advance

IRP researchers led by [Roscoe Brady, M.D.](#), developed a macrophage-targeted glucocerebrosidase, designed to deliver the missing enzyme directly into the macrophages of patients with Gaucher disease. The team conducted the first clinical trial with the new therapy and observed a reversal of all symptoms in all patients.

Impact

Doctors have now established intravenous administration of macrophage-targeted glucocerebrosidase as an effective treatment for the symptoms of Type 1 and Type 3 Gaucher disease¹⁸. For his research, Dr. Brady was awarded the National Medal of Technology and Innovation in 2008, the highest honor for achievement in science and technology bestowed by the U.S. President¹⁹.

Publications

Barton NW, Brady RO, Dambrosia JM, Di Bisceglie AM, Doppelt SH, Hill SC, Mankin HJ, Murray GJ, Parker RI, Argoff CE, et al. [Replacement therapy for inherited enzyme deficiency--macrophage-targeted glucocerebrosidase for Gaucher's disease.](#) *N Engl J Med.* 1991 May 23;324(21):1464-70.

Infections

2013(+): Developing a vaccine for all four dengue viruses

Challenge

Each year, dengue viruses infect 50-100 million people and cause 500,000 hospitalizations worldwide. There are four distinct dengue viruses and, unfortunately, infection from one type does not provide long-term protection against the others. Instead, individuals can develop more severe symptoms upon infection by one of the other viruses. Thus, the ideal dengue vaccine would be tetravalent, i.e., offer protection against all four viruses.

Advance

In January 2013, IRP researchers at the [National Institute of Allergy and Infectious Diseases \(NIAID\)](#) and their colleagues successfully completed a Phase I clinical trial of a group of NIAID-developed tetravalent vaccines and selected one candidate, called TV003, for a Phase II trial. In 90 percent of vaccine recipients, a single dose of TV003 induced immune responses against three or more dengue viruses.

Impact

The NIAID-developed dengue vaccine technology has been licensed by several companies in dengue-endemic regions of South America and Asia. Because it requires only a single dose, TV003 may offer a cost-effective approach to preventing dengue infections worldwide.

Publications

Durbin AP, Kirkpatrick BD, Pierce KK, Elwood D, Larsson CJ, Lindow JC, Tibery C, Sabundayo BP, Shaffer D, Talaat KR, Hynes NA, Wanionek K, Carmolli MP, Luke CJ, Murphy BR, Subbarao K, Whitehead SS. [A single dose of any of four different live attenuated tetravalent dengue vaccines is safe and immunogenic in flavivirus-naïve adults: a randomized, double-blind clinical trial.](#) *J Infect Dis.* 2013 Mar 15;207(6):957-65.

18 <http://www.ninds.nih.gov/disorders/gauchers/gauchers.htm>

19 http://www.ninds.nih.gov/news_and_events/news_articles/pressrelease_20081006_Brady.htm

2013: Discovering a new hepatitis C gene—and its implications for precision medicine

Challenge

Hepatitis C viral (HCV) infection represents a serious threat to public health: up to 150 million individuals are infected worldwide, and as many as 85 percent will develop chronic hepatitis C. Up to five percent of those with chronic hepatitis C may eventually die from liver disease or cancer. Historically, individuals of African descent are less likely to respond to HCV treatment than patients of European or Asian ancestry, suggesting a genetic component to this treatment outcome.

Advance

IRP investigators [Ludmila Prokunina-Olsson, Ph.D.](#), and [Thomas O'Brien, M.D., M.P.H.](#), used RNA sequencing to uncover a new gene, Interferon lambda 4 (IFNL4), that affects the body's ability to overcome HCV infection. Only individuals who carry a specific inherited genetic variant of IFNL4 can produce the IFN- 4 protein, which is strongly associated with a reduced ability to clear the viral infection from the body.

Impact

The gene discovery may help researchers better understand why some people's immune systems do not respond as strongly as others' to clear HCV. In addition, the new genetic marker may better predict HCV treatment outcomes for African-American patients than currently available tests, offering a potential mechanism to improve care in this population and reduce existing health disparities.

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Publications

Prokunina-Olsson L, Muchmore B, Tang W, Pfeiffer RM, Park H, Dickensheets H, Hergott D, Porter-Gill P, Mumy A, Kohaar I, Chen S, Brand N, Tarway M, Liu L, Sheikh F, Astemborski J, Bonkovsky HL, Edlin BR, Howell CD, Morgan TR, Thomas DL, Rehermann B, Donnelly RP, O'Brien TR. [A variant upstream of IFNL3 \(IL28B\) creating a new interferon gene IFNL4 is associated with impaired clearance of hepatitis C virus.](#) *Nat Genet.* 2013 Feb;45(2):164-71.

National Cancer Institute press release – <http://www.cancer.gov/newscenter/newsfromnci/2013/IFNL4affectsclearanceofhepatitisCvirus>

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2013: Investigational malaria vaccine found to be safe and protective

Challenge

Roughly 600,000 people die of malaria each year, most of them infants and children. Malaria transmits to humans through the bite of an infected mosquito, after which infectious malaria parasites travel to the liver, where they multiply and then spread throughout the body. Scientists and healthcare workers have made significant gains in characterizing, treating, and preventing malaria, but a vaccine has remained an elusive goal.

Advance

In a Phase I clinical trial, IRP investigators from the [NIAID Vaccine Research Center](#), in collaboration with [Sanaria Inc.](#), the [Walter Reed Army Institute of Research](#), and the [Navy Medical Research Center](#), evaluated the safety and efficacy of a novel investigational malaria vaccine called PfSPZ. This vaccine includes live, but weakened, malaria parasites, called sporozoites, of the species *Plasmodium falciparum*—the most deadly of the malaria-causing parasites.

Impact

The study showed that a dose-dependent level of protection against malaria can be achieved when the PfSPZ vaccine is administered intravenously. While the results are promising, additional work is required to evaluate the vaccine in more people and to optimize the dose, schedule, and delivery to determine whether it confers long-lasting protection.

Publications

Seder RA, Chang LJ, Enama ME, Zephir KL, Sarwar UN, Gordon IJ, Holman LA, James ER, Billingsley PF, Gunasekera A, Richman A, Chakravarty S, Manoj A, Velmurugan S, Li M, Ruben AJ, Li T, Eappen AG, Stafford RE, Plummer SH, Hendel CS, Novik L, Costner PJ, Mendoza FH, Saunders JG, Nason MC, Richardson JH, Murphy J, Davidson SA, Richie TL, Sedegah M, Sutamihardja A, Fahle GA, Lyke KE, Laurens MB, Roederer M, Tewari K, Epstein JE, Sim BK, Ledgerwood JE, Graham BS, Hoffman SL; VRC 312 Study Team. [Protection against malaria by intravenous immunization with a nonreplicating sporozoite vaccine](#). *Science*. 2013 Sep 20;341(6152):1359-65.

2013: Seeing the shape of hepatitis B's action

Challenge

The World Health Organization estimates that the hepatitis B virus has infected two billion people around the world, and about 600,000 people die every year due to consequences of infection²⁰. A vaccine has existed since 1982, but there is no cure for already infected individuals, only complex and costly treatments.

Advance

IRP investigators led by [Alasdair Steven, Ph.D.](#), and [Paul Wingfield, Ph.D.](#), deciphered the atomic structure of the e-antigen protein, a key hepatitis B virus immune-regulator suspected in helping to establish chronic infection.

Impact

Revealing the complex structure of the e-antigen protein provides clues to how the hepatitis B virus eludes the immune system so successfully, which may lead to better treatments.

Publications

Dimattia MA, Watts NR, Stahl SJ, Grimes JM, Steven AC, Stuart DI, Wingfield PT. [Antigenic switching of hepatitis B virus by alternative dimerization of the capsid protein](#). *Structure*. 2013 Jan 8;21(1):133–142.

2012: Can we outwit the influenza virus with a universal vaccine?

Challenge

A master of disguise, the influenza virus presents unique strains, or versions, of itself each season through its ability to mutate, rendering vaccines developed for particular strains ineffective against new viruses. A universal influenza vaccine could provide people with broad and long-lasting flu protection. But researchers did not know if the presence of existing antibodies—formed in response to a bout with the flu or a vaccination—would interfere with the efficacy of a universal vaccine.

Advance

IRP researchers led by [Gary J. Nabel, M.D., Ph.D.](#), tested if a prime-boost vaccination schedule would be negatively affected by the presence of existing antibodies. They found that animals receiving a special prime-boost vaccine regimen were still able to produce broadly neutralizing antibodies, regardless of pre-existing immunity.

Impact

Further development and testing of a universal human influenza vaccine to provide broad and long-lasting protection against multiple influenza virus strains is underway. If successful, an approved universal influenza vaccine could save billions of dollars and, more importantly, millions of lives.

Publications

Press Release - NIH Study Suggests Potential Hurdle to Universal Flu Vaccine Development May Be Overcome: <http://www.niaid.nih.gov/news/newsreleases/2012/Pages/broadFluAntibodies.aspx>.

Wei CJ, Yassine HM, McTamney PM, Gall JG, Whittle JR, Boyington JC, Nabel GJ. [Elicitation of broadly neutralizing influenza antibodies in animals with previous influenza exposure](#). *Sci Transl Med*. 2012 Aug 15;4(147):147ra114.

2012: Identifying a promising HIV vaccine target

Challenge

An important goal of HIV vaccine research is to identify what part of the virus to target. For decades, researchers have looked for regions of HIV that can induce antibodies able to neutralize multiple strains of the virus.

Advance

In late 2012, IRP researchers from the [National Institute of Allergy and Infectious Diseases](#) and their colleagues reported the isolation of an antibody called 10E8 from an HIV-infected patient. The team found that the 10E8 antibody neutralizes approximately 98 percent of HIV strains tested, and they identified the specific part of the virus that 10E8 targets.

Impact

Unlike previously described HIV antibodies, 10E8 is not autoreactive—meaning it does not react to the body's own cells—an important requirement for vaccines. This work suggests that an HIV vaccine that induces 10E8-like antibodies might be effective, offering hope for preventing an infection that has killed more than 25 million people worldwide. The 10E8 monoclonal antibody is now offered for commercial licensing applications via the [NIH Office of Technology Transfer](#).

Publications

Huang J, Ofek G, Laub L, Louder MK, Doria-Rose NA, Longo NS, Imamichi H, Bailer RT, Chakrabarti B, Sharma SK, Alam SM, Wang T, Yang Y, Zhang B, Migueles SA, Wyatt R, Haynes BF, Kwong PD, Mascola JR, Connors M. [Broad and potent neutralization of HIV-1 by a gp41-specific human antibody](#). *Nature*. 2012 Nov 15;491(7424):406-12.

2012: Visualizing a viral infection as it happens

Challenge

Retroviruses, such as the human immunodeficiency virus (HIV), initiate infection when the viral membrane fuses with host cells, a process mediated by viral proteins and cellular receptors. But scientists need a more detailed understanding of the mechanism in order to develop drugs that can impede the fusion.

Advance

IRP researchers led by [Alasdair Steven, Ph.D.](#), used cryo-electron tomography (cryo-ET), a technique that allows three-dimensional imaging of individual virus particles at molecular resolution, to visualize successive stages of virus-host cell fusion in a bird retrovirus model. They succeeded in viewing a specific “pre-hairpin” conformation of the interaction, a long hypothesized key intermediate of fusion that had never been directly visualized.

Impact

This discovery has informed many advanced investigations of fusion dynamics, including those of other retroviruses, such as HIV and the influenza virus, which infect by a similar mechanism.

Publications

Cardone G, Brecher M, Fontana J, Winkler DC, Butan C, White JM, Steven AC. [Visualization of the two-step fusion process of the retrovirus avian sarcoma/leukosis virus by cryo-electron tomography](#). *J Virol*. 2012 Nov;86(22):12129-37.

2011: Understanding bacterial immune systems

Challenge

Bacteria have extremely diverse and rapidly evolving antiviral defense systems that remain poorly understood. Without more detailed characterization of these systems and the evolutionary dynamics of bacteria, doctors would continue struggling against the development and spread of antibiotic-resistant bacterial strains.

Advance

IRP researchers led by [Eugene Koonin, Ph.D.](#), developed an evolutionary classification of bacterial adaptive immunity systems. Koonin and colleagues then created a mathematical model of virus-host co-evolution that identifies conditions under which bacteria maintain or lose adaptive immunity.

Impact

Microbiologists quickly adopted the new classification of bacterial immunity systems as a framework for research in the field. Researchers can use the mathematical model of virus-host co-evolution to predict bacteriophage resistance and antibiotic resistance.

Publications

Makarova KS, Haft DH, Barrangou R, Brouns SJ, Charpentier E, Horvath P, Moineau S, Mojica FJ, Wolf YI, Yakunin AF, van der Oost J, Koonin EV. [Evolution and classification of the CRISPR-Cas systems](#). *Nat Rev Microbiol*. 2011 Jun;9(6):467-77.

Weinberger AD, Wolf YI, Lobkovsky AE, Gilmore MS, Koonin EV. [Viral diversity threshold for adaptive immunity in prokaryotes](#). *MBio*. 2012 Dec 4;3(6):e00456-12.

2010(+): Illuminating a path toward HIV vaccine development

Challenge

Since the discovery of the human immunodeficiency virus (HIV) in 1984, advances in antiretroviral therapy have helped control HIV progression around the world and, in several developed countries, turned a fatal illness into a chronic disease. But current therapies cannot entirely clear HIV from the body, highlighting the need for an effective vaccine.

Advance

Tongqing Zhou, Ph.D., and colleagues in the laboratory of [Peter Kwong, Ph.D.](#), identified a broadly neutralizing HIV antibody they called VRC01. Only about 20 percent of people can naturally generate these types of protective HIV antibodies. The researchers went on to map how the HIV virus co-evolved with broadly neutralizing antibodies in a single HIV-positive person.

Impact

By understanding the simultaneous evolution of HIV and its antibodies, scientists may eventually be able to create a blueprint for the development of an HIV vaccine that can induce broadly neutralizing HIV antibodies in the general population.

Publications

Press Release - NIH Scientists, Grantees Map Possible Path to an HIV Vaccine:

<http://www.niaid.nih.gov/news/newsreleases/2013/Pages/HIVvaccinePath.aspx>.

Zhou T, Georgiev I, Wu X, Yang ZY, Dai K, Finzi A, Kwon YD, Scheid JF, Shi W, Xu L, Yang Y, Zhu J, Nussenzweig MC, Sodroski J, Shapiro L, Nabel GJ, Mascola JR, Kwong PD. [Structural basis for broad and potent neutralization of HIV-1 by antibody VRC01](#). *Science*. 2010 Aug 13;329(5993):811-7.

Wu X, Yang ZY, Li Y, Hogerthorp CM, Schief WR, Seaman MS, Zhou T, Schmidt SD, Wu L, Xu L, Longo NS, McKee K, O'Dell S, Louder MK, Wycuff DL, Feng Y, Nason M, Doria-Rose N, Connors M, Kwong PD, Roederer M, Wyatt RT, Nabel GJ, Mascola JR. [Rational design of envelope identifies broadly neutralizing human monoclonal antibodies to HIV-1](#). *Science*. 2010 Aug 13;329(5993):856-61.

Wu X, Zhou T, Zhu J, Zhang B, Georgiev I, Wang C, Chen X, Longo NS, Louder M, McKee K, O'Dell S, Perfetto S, Schmidt SD, Shi W, Wu L, Yang Y, Yang ZY, Yang Z, Zhang Z, Bonsignori M, Crump JA, Kapiga SH, Sam NE, Haynes BF, Simek M, Burton DR, Koff WC, Doria-Rose NA, Connors M; NISC Comparative Sequencing Program, Mullikin JC, Nabel GJ, Roederer M, Shapiro L, Kwong PD, Mascola JR. [Focused evolution of HIV-1 neutralizing antibodies revealed by structures and deep sequencing](#). *Science*. 2011 Sep 16;333(6049):1593-602.

Liao HX, Lynch R, Zhou T, Gao F, Alam SM, Boyd SD, Fire AZ, Roskin KM, Schramm CA, Zhang Z, Zhu J, Shapiro L; NISC Comparative Sequencing Program, Becker J, Benjamin B, Blakesley R, Bouffard G, Brooks S, Coleman H, Dekhtyar M, Gregory M, Guan X, Gupta J, Han J, Hargrove A, Ho SL, Johnson T, Legaspi R, Lovett S, Maduro Q, Masiello C, Maskeri B, McDowell J, Montemayor C, Mullikin J, Park M, Riebow N, Schandler K, Schmidt B, Sison C, Stantripop M, Thomas J, Thomas P, Vemulapalli M, Young A, Mullikin JC, Gnanakaran S, Hraber P, Wiehe K, Kelsoe G, Yang G, Xia SM, Montefiori DC, Parks R, Lloyd KE, Searce RM, Soderberg KA, Cohen M, Kamanga G, Louder MK, Tran LM, Chen Y, Cai F, Chen S, Moquin S, Du X, Joyce MG, Srivatsan S, Zhang B, Zheng A, Shaw GM, Hahn BH, Kepler TB, Korber BT, Kwong PD, Mascola JR, Haynes BF. [Co-evolution of a broadly neutralizing HIV-1 antibody and founder virus](#). *Nature*. 2013 Apr 3;doi: 10.1038/nature12053.

2001(+): Identifying and understanding rare immune system diseases

Challenge

Primary immune deficiency diseases (PIDDs) are rare difficult-to-manage disorders caused by inherited defects in cells of the immune system²¹. They can result in increased risk of life-threatening infections, autoimmune diseases, and tumors²². Understanding the molecular mechanisms underlying these immunodeficiencies is crucial to therapeutic decision-making and effective management of each disease.

Advance

For more than 30 years, IRP investigators at the [National Institute of Allergy and Infectious Diseases \(NIAID\)](#) have studied and developed new treatments for known PIDDs and worked to decipher immunodeficiencies of unknown etiology. In the last few years alone, IRP scientists identified:

- NEMO immunodeficiency, which leads to frequent bacterial and viral infections and abnormal teeth, hair, skin, and nails
- DOCK8 immunodeficiency, which can cause persistent skin infections, allergies, and cancer
- XMEN disease, characterized by persistent Epstein-Barr virus infections and magnesium deficiency
- PLAID, characterized by immune deficiency, autoimmunity, inflammatory skin disorders, and cold-induced hives

Impact

IRP researchers and their collaborators have made significant contributions to current understanding of PIDDs and to the treatment of patients affected by these devastating diseases. In 2007, NIAID opened a [Primary Immune Deficiency Clinic at the NIH Clinical Center](#) to provide a focus of IRP expertise for referring physicians and their patients. The clinic accepts patients with known or suspected PIDDs and offers treatment recommendations and, in some cases, a disease diagnosis.

Publications

Press Release – NIAID Initiative Addresses Primary Immune Deficiency Diseases:

<http://www.niaid.nih.gov/news/newsreleases/2003/Pages/pirc.aspx>.

Jain A, Ma CA, Liu S, Brown M, Cohen J, Strober W. [Specific missense mutations in NEMO result in hyper-IgM syndrome with hypohydrotic ectodermal dysplasia](#). *Nat Immunol*. 2001 Mar;2(3):223-8.

Zhang Q, Davis JC, Lamborn IT, Freeman AF, Jing H, Favreau AJ, Matthews HF, Davis J, Turner ML, Uzel G, Holland SM, Su HC. [Combined immunodeficiency associated with DOCK8 mutations](#). *N Engl J Med*. 2009 Nov 19;361(21):2046-55.

21 <http://www.niaid.nih.gov/topics/immuneDeficiency/Understanding/Pages/quickFacts.aspx>

22 <http://www.niaid.nih.gov/about/yearinreview/advances/scientificFindings/Pages/AddressingImmuneMediatedDiseases.aspx>

23 <http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/hepa.pdf>

24 <http://www.cdc.gov/hepatitis/HAV/HAVfaq.htm#general>

1995: In the fight against viral hepatitis A, vaccines save lives

Challenge

The hepatitis A virus causes contagious, acute inflammation of the liver. Prior to the discovery of a vaccine, an estimated 100 people died from it every year in the United States²³. With no treatments, creating a vaccine against the hepatitis A virus could reduce incidence of the disease and save lives²⁴.

Advance

IRP researchers Robert Purcell, M.D., Albert Kapikian, M.D., Stephen Feinstone, M.D., and colleagues played a crucial role in developing the first licensed hepatitis A vaccine, from initial identification and characterization of the virus to the clinical trials that demonstrated protective efficacy²⁵.

Impact

The discovery and development of hepatitis A vaccines were landmark moments for public health, providing nearly 100 percent of adults with protective levels of antibodies, and contributing to the decline of hepatitis A rates in the U.S. by 92 percent since 1995²⁶.

Publications

NIAD's Role in Hepatitis Research: <http://www.niaid.nih.gov/topics/hepatitis/research/Pages/introduction.aspx>.

SM Feinstone, AZ Kapikian, RH Purcell. [Hepatitis A: detection by immune electron microscopy of a viruslike antigen associated with acute illness](#). *Science*. 1973 Dec 7;182(116):1026–8.

Daemer RJ, Feinstone SM, Gust ID, Purcell RH. [Propagation of human hepatitis A virus in African green monkey kidney cell culture: primary isolation and serial passage](#). *Infect Immun*. 1981 Apr;32(1):388–93.

K Van Herck, P Van Damme. [Prevention of hepatitis A by Havrix: a review](#). *Expert Rev Vaccines*. 2005 Aug;4(4):459–71.

1989: Protecting at-risk children from a severe respiratory disease

Challenge

Respiratory syncytial virus (RSV) is a leading cause of bronchiolitis and pneumonia in children less than one year old²⁷. RSV infection can be life-threatening, especially for babies born prematurely or with health problems such as chronic lung disease or congenital heart disease²⁸. An effective means to prevent severe RSV disease was needed.

Advance

IRP investigators Robert M. Chanock, M.D., Brian Murphy, M.D., and colleagues showed that giving anti-RSV antibodies to animals protected them from RSV infection. The researchers then developed a monoclonal antibody that neutralized RSV in animal models. The pharmaceutical company MedImmune licensed the monoclonal antibody, further developed it for human use, and conducted clinical trials showing that it could protect high-risk infants from severe RSV disease.

25 <http://www.ncbi.nlm.nih.gov/pubmed/8182274>

26 <http://www.cdc.gov/hepatitis/HAV/HAVfaq.htm#general>

27 <http://www.cdc.gov/rsv/about/faq.html>

28 <http://www.cdc.gov/rsv/about/faq.html>

29 <http://pediatrics.aappublications.org/content/112/6/1442.full.pdf>

Impact

Following FDA approval in 1998, MedImmune marketed the RSV antibody Synagis® for prevention of severe RSV disease in high-risk infants. Monthly administration of Synagis during RSV season reduces RSV-related hospitalizations by an estimated 45 to 55 percent²⁹. Because RSV is an important pediatric pathogen and an increasingly recognized cause of severe respiratory disease in chronically ill adults and the elderly, RSV vaccine research and development continues to be a high priority in the IRP.

Publications

Prince GA, Hemming VG, Horswood RL, Chanock RM. [Immunoprophylaxis and immunotherapy of respiratory syncytial virus infection in the cotton rat](#). *Virus Res*. 1985 Oct;3(3):193-206.

Murphy BR, Sotnikov A, Paradiso PR, Hildreth SW, Jenson AB, Baggs RB, Lawrence L, Zubak JJ, Chanock RM, Beeler JA, et al. [Immunization of cotton rats with the fusion \(F\) and large \(G\) glycoproteins of respiratory syncytial virus \(RSV\) protects against RSV challenge without potentiating RSV disease](#). *Vaccine*. 1989 Dec;7(6):533-40.

1985(+): Hitting HIV hard with HAART therapy

Challenge

The human immunodeficiency virus (HIV), discovered in 1984³⁰, is a retrovirus that causes progressive failure of the immune system, resulting in the development of opportunistic infections and cancers (acquired immunodeficiency syndrome, or AIDS). Development of therapies is imperative to stop viral replication and progression of the disease.

Advance

Soon after HIV was found to be the cause of AIDS, IRP researchers [Samuel Broder, M.D.](#), [Hiroaki Mitsuya, M.D., Ph.D.](#), and [Robert Yarchoan, M.D.](#), demonstrated that certain nucleoside reverse transcriptase inhibitors had activity against HIV in the test tube, a discovery the team rapidly moved to test in clinical trials.

Impact

This research yielded the first drugs approved by the U.S. FDA for the treatment of HIV infection: zidovudine (AZT) in 1985, didanosine (ddI) in 1991, and zalcitabine (ddC) in 1992. These drugs became the foundation for highly active antiretroviral therapies (HAART), saving countless lives.

Publications

Yarchoan R, Mitsuya H, Thomas RV, Pluda JM, Hartman NR, Perno CF, Marczyk KS, Allain JP, Johns DG, Broder S. [In vivo activity against HIV and favorable toxicity profile of 2',3'-dideoxyinosine](#). *Science*. 1989 Jul 28;245(4916):412-5.

1974(+): Developing the first rotavirus vaccine

Challenge

Rotaviruses are the most common cause of severe childhood diarrhea worldwide. They are responsible for up to 500,000 deaths each year. To reduce their deadly effect, scientists needed to better understand the virus and apply that knowledge to developing a vaccine.

Advance

IRP researchers led by Albert Kapikian, M.D., first identified human rotavirus in the United States in 1974. The team defined the virus' mode of transmission and pinpointed the proteins critical for triggering an immune response. Their efforts, in partnership with Wyeth-Ayerst Laboratories, led to the development, testing, and 1998 FDA approval of RotaShield, the first rotavirus vaccine.

Impact

While RotaShield is no longer in use, the researchers' decades-long effort carried basic research results all the way through to the development of a vaccine. The knowledge derived from their process paved the way for the creation of second-generation rotavirus vaccines, which are now being licensed for use in low-income countries.

Publications

Kapikian AZ, Kim HW, Wyatt RG, Rodriguez WJ, Ross S, Cline WL, Parrott RH, Chanock RM. [Reoviruslike agent in stools: association with infantile diarrhea and development of serologic tests.](#) *Science*. 1974 Sep 20;185(4156):1049-53.

Further reading: <http://www.niaid.nih.gov/topics/rotavirus/Pages/rotavirusVaccine.aspx>



procedures

Procedures and Therapies

2013: Protecting salivary glands from irradiation damage

Challenge

Each year, more than 500,000 patients worldwide are treated for head and neck cancer. The current standard of care involves exposure to radiation that can damage salivary glands, leading to permanent dry mouth (xerostomia) that negatively affects oral health and overall quality of life.

Advance

IRP scientists led by [Matthew Hoffman, B.D.S., Ph.D.](#), showed that treating irradiated mouse fetal salivary gland tissues with the neurotrophic protein neurturin to restore parasympathetic function improves salivary gland regeneration.

Impact

The findings provide a new target and research direction for how salivary glands (and other sensitive organs) may be protected or regenerated in people undergoing extensive treatment for cancers.

Publications

Knox SM, Lombaert IM, Haddox CL, Abrams SR, Cotrim A, Wilson AJ, Hoffman MP. [Parasympathetic stimulation improves epithelial organ regeneration](#). *Nat Commun*. 2013;4:1494.

2013: Visualizing chromosomal translocations in living cells

Challenge

When part of a chromosome breaks off and becomes attached to another chromosome—an abnormality called a chromosomal translocation—cells can quickly become uncontrolled, leading to excessive growth or cancer. However, because these events are very rare, it has been extremely difficult to study them.

Advance

IRP scientists led by [Tom Misteli, Ph.D.](#), used an experimental imaging system developed at the [National Cancer Institute \(NCI\)](#) to track fluorescently labeled chromosomes in thousands of mouse cells following induced breaks in their DNA. Though the vast majority of chromosomes reattached correctly, the researchers were able to capture time-lapse video of translocations, allowing them to visualize and identify several previously unknown distinct steps and proteins involved in the process.

Impact

Dr. Misteli's new live-cell imaging technique now allows researchers to investigate rare chromosomal abnormalities. With a better understanding of how chromosomal translocations occur, there is potential to identify new therapeutic targets that might prevent the development of many types of cancer.

Publications

Roukos V, Voss TC, Schmidt CK, Lee S, Wangsa D, Misteli T. [Spatial Dynamics of Chromosome Translocations in Living Cells](#). *Science*. 2013 Aug 9;341(6146):660-4.

2013: Visualizing DNA repair in action

Challenge

DNA polymerase plays a central role in repairing damaged DNA, making this enzyme a key regulator of genome stability and likely protector against cancer and degenerative diseases. More information about DNA polymerase's functions and interactions with other molecules is essential to better leverage genome repair mechanisms in developing new therapies.

Advance

IRP researchers led by [Samuel H. Wilson, M.D.](#), used a new time-lapse crystallography approach to capture and visualize real-time DNA polymerase activity during DNA synthesis and repair.

Impact

Dr. Wilson's time-lapse snapshots provide novel insight into how DNA polymerase chooses the correct base when repairing DNA. The images also revealed specific features of the enzyme that are now considered therapeutic targets for regulating repair after stress-induced DNA damage.

Publications

Freudenthal BD, Beard WA, Shock DD, Wilson SH. [Observing a DNA polymerase choose right from wrong](#). *Cell*. 2013 Jul 3;154(1):157-68.

2012: Exposing “silent” heart attacks through novel imaging techniques

Challenge

Each year, about 1.2 million people in the U.S. have heart attacks³¹, but not all heart attacks are visible with electrocardiography (EKG). Rapid and accurate methods to detect and manage “silent” heart attacks are needed to speed diagnosis and ensure timely treatment.

Advance

IRP scientists led by [Andrew E. Arai, M.D.](#), pioneered the use of non-invasive magnetic resonance imaging (MRI) to accurately detect and respond to unrecognized myocardial infarctions.

Impact

For the first time, physicians are able to detect, monitor, and treat heart attacks that patients may not even know had occurred. Early intervention in this type of cardiac damage can reduce the likelihood of subsequent cardiac events, including heart failure.

Publications

Schelbert EB, Cao JJ, Sigurdsson S, Aspelund T, Kellman P, Aletras AH, Dyke CK, Thorgeirsson G, Eiriksdottir G, Launer LJ, Gudnason V, Harris TB, Arai AE. [Prevalence and Prognosis of Unrecognized Myocardial Infarction Determined by Cardiac Magnetic Resonance in Older Adults](#). *JAMA*. 2012;308(9):890-896.

2012: Medical radiation and cancer: minimizing the risk from CT scans

Challenge

Ionizing radiation is a known carcinogen. Many medical imaging tests employ ionizing radiation to capture detailed pictures of internal organs for diagnosing injury or disease. Radiation-related cancer risk from the scans is small at the individual level, however, small risks could result in a large number of future cancers in the total U.S. population. Because of the increasing use of computed tomographic (CT) scans in the U.S. (in 2007 the average was 70 million scans annually), it is important to discern which type of scans—and the ages at which they are given—contribute most to overall cancer risk.

Advance

IRP researchers led by [Amy Berrington de Gonzalez, D.Phil.](#), estimated that 29,000 future cancers could be related to CT scans performed in the U.S. in 2007 alone. They found that the largest contribution to cancer risk comes from the scans of the abdomen/pelvis, chest, head, and whole body.

Impact

Following the research results, the [NIH Clinical Center](#) updated its protocol to require documentation of the ionizing radiation dosage received for each CT scan, and professional groups in the U.S. and overseas have adjusted their guidelines, especially for pediatric use of CT. Between 2011 and 2013, CT procedure volume dropped 11% in the U.S., with about 10 million fewer scans.

31 <http://www.nhlbi.nih.gov/health/health-topics/topics/heartattack/>

Publications

Berrington de G, Mahesh M, Kim KP, Bhargavan M, Lewis R, Mettler F, Land C. [Projected cancer risks from computed tomographic scans performed in the United States in 2007](#). *Arch Intern Med*. 2009 Dec 14;169(22):2071-7.

Pearce M, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, Howe NL, Ronckers CM, Rajaraman P, Sir Craft AW, Parker L, Berrington de González A. [Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study](#). *Lancet*. 2012 Aug 4;380(9840):499-505.

2012: Open your eyes to the power of image-based online searching

Challenge

Illustrations in medical literature contribute greatly to understanding complex biomedical concepts—for researchers, scientists, and the lay public alike. However, bibliographic databases are mostly text-based; hence the need for systems that deliver citations enriched by visual material, for example, radiographic images, photographs, sketches, graphs or charts.

Advance

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Impact

As the first production-quality system of its kind in the biomedical domain, Open-i enables medical professionals and the public to access both highly relevant visual information and key outcome statements from biomedical publications. Just a few months after public release, the site had more than 5,000 unique visitors per day and was ranked 382nd in the world (among 30 million Web sites)³².

Publications

The Open-i Website: <http://openi.nlm.nih.gov/index.php>.

2012: Visualizing coronary artery disease

Challenge

Coronary artery disease (CAD) is the most common type of heart disease and the leading cause of death in the United States, responsible for 400,000 deaths each year³³. Currently, no single test can detect CAD³⁴.

Advance

IRP researchers Khaled Abd-Elmoniem, Ph.D., and Ahmed Gharib, M.D., developed a more sensitive way to obtain images of the coronary vessel wall. The new technique is called “time-resolved acquisition of phase-sensitive dual-inversion recovery” (TRAPD) imaging and produces higher-quality results than conventional single-image methods.

32 <http://www.webstatsdomain.com/domains/openi.nlm.nih.gov>

33 <http://www.nhlbi.nih.gov/health/health-topics/topics/cad/atrisk.html/>

34 <http://www.nhlbi.nih.gov/health/health-topics/topics/cad/diagnosis.html>

Impact

TRAPD imaging provides better arterial wall visualization and quantitative assessments of coronary arteries, allowing for sensitive vessel wall thickness measurements that can distinguish CAD risk factors. The technique could eventually help identify individuals at risk for CAD and allow earlier access to treatments that relieve symptoms, reduce complications, and save lives.

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Publications

Abd-Elmoniem KZ, Gharib AM, Pettigrew RI. [Coronary vessel wall 3-T MR imaging with time-resolved acquisition of phase-sensitive dual inversion-recovery \(TRAPD\) technique: initial results in patients with risk factors for coronary artery disease.](#) *Radiology*. 2012 Dec;265(3):715-23.

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2011: Advancing rapid detection of prion diseases

Challenge

Prion diseases, such as Creutzfeldt-Jacob disease (CJD) in humans, scrapie in sheep, and mad cow disease in cattle, are difficult to diagnose, currently untreatable, and ultimately fatal. People and animals can be infected for years before symptoms appear. A faster and more practical prion diagnostic test that does not require cerebrospinal fluid sampling or brain tissue could simplify screening for prion diseases and allow earlier diagnostic confirmation to guide healthcare decision-making.

Advance

IRP scientists led by [Byron Caughey, Ph.D.](#), developed a prion blood test called enhanced Quaking-Induced Conversion (eQuIC), which uses an antibody to isolate abnormal prion protein from blood plasma and then amplifies it to enhance detection. The test is 10,000 times more sensitive for detecting variant CJD than previously described tests. [The National Institute of Allergy and Infectious Diseases \(NIAID\)](#) and its project partner, Swiss diagnostics firm Prionics AG, have applied for a patent on the eQuIC test.

Impact

eQuIC could be used by blood banks, hospitals, livestock operations, and rendering plants to screen for prion diseases in a far more efficient and less invasive manner than current diagnostic tools. Additionally, this concept of testing for abnormal proteins could eventually be applied to the diagnosis of other diseases, such as Alzheimer's, Huntington's, and Parkinson's disease, but more research is needed and underway.

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Publications

Orrú CD, Wilham JM, Raymond LD, Kuhn F, Schroeder B, Raeber AJ, Caughey B. [Prion disease blood test using immunoprecipitation and improved quaking-induced conversion.](#) *MBio*. 2011 May 10;2(3):e00078-11.

.....

2011: Pioneering closed-chest hole-in-the-heart repair

Challenge

One of the most common congenital heart diseases is ventricular septal defect, or "hole-in-the-heart." Current repair techniques require open-chest surgery and prolonged exposure to ionizing radiation to visualize the appropriate anatomy. Non-surgical interventions would reduce risks and improve recovery times.

Advance

Robert J. Lederman, M.D., and colleagues tested a pre-clinical MRI-guided, catheter-based, closed-chest intervention that provides enhanced image guidance, reduced radiation exposure, and reduced surgical risk.

Impact

If clinical trials continue to support development of MRI-guided treatments, pediatric patients with ventricular septal defect could avoid the risks associated with traditional surgical interventions in favor of a less invasive and safer procedure.

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Publications

Ratnayaka K, Saikus CE, Faranesh AZ, Bell JA, Barbash IM, Kocaturk O, Reyes CA, Sonmez M, Schenke WH, Wright VJ, Hansen MS, Slack MC, Lederman RJ. [Closed-chest transthoracic magnetic resonance imaging-guided ventricular septal defect closure in swine](#). *JACC Cardiovasc Interv*. 2011 Dec;4(12):1326-34.

.....

2011: Taking the random out of biopsy sampling

Challenge

Biopsy is currently the only way to confirm a diagnosis of prostate cancer. However, despite improvements in technology, prostate biopsy sampling remains a challenge, and cancerous lesions may be missed. Novel diagnostic tools are needed to ensure more accurate biopsies and better cancer detection rates.

Advance

Peter L. Choyke, M.D., Peter A. Pinto, M.D., Bradford Wood, M.D., and colleagues developed a combined magnetic resonance imaging (MRI) and ultrasound-guided prostate biopsy, a minimally invasive technique that allows for the detection of cancer at a far higher rate than current biopsy techniques.

Impact

Fusion MRI/ultrasound-guided biopsy has been shown in clinical trials to detect more instances of cancer than standard biopsies, consequently leading to more accurate diagnosis and more appropriate course of treatment for cancer patients.

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Publications

Turkbey B, Xu S, Kruecker J, Locklin J, Pang Y, Shah V, Bernardo M, Baccala A, Rastinehad A, Benjamin C, Merino MJ, Wood BJ, Choyke PL, Pinto PA. [Documenting the location of systematic transrectal ultrasound-guided prostate biopsies: correlation with multi-parametric MRI](#). *Cancer Imaging*. 2011 Mar 29;11:31-6.

.....

2010: The Teaching Tool: A digital cervix for colposcopists

Challenge

Colposcopy—examination of the cervix with a specialized microscope—is a widely used diagnostic technique for cervical cancer, a disease that affects nearly a quarter of a million women in the United States³⁵. There is an ongoing need for effective knowledge assessment in this area, both for medical professionals in training and working clinicians seeking to advance their skills. Since colposcopy is image-based, an image-based assessment allowing for interaction with the images would be ideal.

Advance

IRP researchers led by [Rodney Long, M.A.](#), in collaboration with colleagues at the [American Society for Colposcopy and Cervical Pathology \(ASCCP\)](#), have developed the Teaching Tool, an interactive online assessment system for medical professionals in the field of colposcopy. This system uses cervicography images to simulate views of the uterine cervix as seen through a colposcope, and includes two assessment exams given by the ASCCP: one for medical professionals in training, and the other for established clinicians.

Impact

Since its release in 2010, the Teaching Tool has been used nationwide in more than 100 Resident Programs in Ob/Gyn and Family Practice, and at institutions such as the Mayo Clinic, Georgetown University, Baylor College of Medicine, and Duke University Medical Center. The tool has been used to give more than 1,000 exams to physicians in training and over 200 established medical professionals who use colposcopy in their practices.

Publications

The Teaching Tool: <http://infocus.nlm.nih.gov/2012/04/innovative-collaboration-produ.html>.

2009: How voltage ion channels interact with their surroundings

Challenge

Voltage-activated ion channels are important to a variety of physiological processes, including generating nerve impulses, regulating heart contraction, and secreting hormones. Visualizing ion channels in their native environments—for example, within a lipid bilayer—is a technical challenge that if overcome could reshape treatments for many diseases.

Advance

IRP researchers led by [Kenton Swartz, Ph.D.](#), used neutron diffraction, solid-state nuclear magnetic resonance (NMR) spectroscopy, and molecular dynamics simulations to gather new information about voltage-activated ion channels, discovering interactions with the surrounding membrane in a way that maintains both the charged nature of the channel and the integrity of the membrane.

Impact

The findings provide perspective for voltage sensors and a new direction for targeted therapeutic development, since many drugs that affect the nervous system work by modifying the behavior of voltage-activated ion channels.

Publications

Krepkiy D, Mihailescu M, Freitas JA, Schow EV, Worcester DL, Gawrisch K, Tobias DJ, White SH, Swartz KJ. [Structure and hydration of membranes embedded with voltage-sensing domains](#). *Nature*. 2009 Nov 26;462(7272):473-9.

2008(+): Diseases with no diagnosis: Providing relief for the rare and unknown

Challenge

For individuals with rare and unknown diseases, there is no greater goal than an accurate diagnosis leading to possibilities of therapeutic relief. Doctors and scientists have long recognized the path to diagnosis as an opportunity to learn more about human disease. A program aimed at providing answers and insight could help both patients and researchers.

Advance

The [NIH Undiagnosed Diseases Program \(UDP\)](#) was established in 2008 and has since seen more than 150 patients a year. The success of the program is illustrated best through the discovery and diagnosis of rare disorders, such as when [William A. Gahl, M.D., Ph.D.](#), and colleagues uncovered a rare arterial calcification disease. By conducting clinical, radiographic and genetic studies in three families, the researchers eventually identified a novel gene mutation that causes a protein deficiency.

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The UDP has received thousands of applications since opening, with approximately 10 percent of the program's patients receiving a full diagnosis, and a further 30 percent gaining partial diagnosis. The researchers of the UDP continue to work tirelessly to discover the cause of those ailments still undiagnosed, along the way finding new biochemical, genetic and molecular pathways, and furthering our knowledge of human disease.

Publications

NIH Launches Undiagnosed Diseases Program: <http://www.genome.gov/27026388>.

St Hilaire C, Ziegler SG, Markello TC, Brusco A, Groden C, Gill F, Carlson-Donohoe H, Lederman RJ, Chen MY, Yang D, Siegenthaler MP, Arduino C, Mancini C, Freudenthal B, Stanescu HC, Zdebik AA, Chaganti RK, Nussbaum RL, Kleta R, Gahl WA, Boehm M. [NT5E mutations and arterial calcifications](#). *N Engl J Med*. 2011 Feb 3;364(5):432-42.

2006(+): Inventing sharper and faster optical microscopes for live cell imaging

Challenge

Microscopes have traditionally evolved in tandem with medical research, and scientists today need new generations of microscopes to enable them to delve even deeper into the molecular mechanisms of disease.

Advance

IRP investigators, including [Clare M. Waterman, Ph.D.](#), [Jennifer Lippincott-Schwartz, Ph.D.](#), and [Hari Shroff, Ph.D.](#), have pioneered new imaging techniques and tools, such as fluorescent speckle microscopy (FSM), photoactivation localization microscopy (PALM), and inverted selective plane illumination microscopy (iSPIM), that provide dramatically clearer views of healthy and diseased live cells, their organelles, and the protein interactions within.

Impact

Through improved imaging, researchers around the world can now visualize complex developmental and disease progressions that previously could only be conjectured. The ability to visualize cellular organelles and macromolecules in such fine detail provides researchers with new tools to accelerate understanding of cellular function in health and disease.

Publications

Kanchanawong P, Shtengel G, Pasapera AM, Ramko EB, Davidson MW, Hess HF, Waterman CM. [Nanoscale architecture of integrin-based cell adhesions](#). *Nature*. 2010 Nov 25;468(7323):580-4.

Betzig E, Patterson GH, Sougrat R, Lindwasser OW, Olenych S, Bonifacino JS, Davidson MW, Lippincott-Schwartz J, Hess HF. [Imaging intracellular fluorescent proteins at nanometer resolution](#). *Science*. 2006 Sep 15;313(5793):1642-5. Epub 2006 Aug 10.

Wu Y, Ghitani A, Christensen R, Santella A, Du Z, Rondeau G, Bao Z, Colón-Ramos D, Shroff H. [Inverted selective plane illumination microscopy \(iSPIM\) enables coupled cell identity lineaging and neurodevelopmental imaging in *Caenorhabditis elegans*](#). *PNAS*. 2011 Oct 25;108(43):17708-13. doi: 10.1073/pnas.1108494108. Epub 2011 Oct 17.

2002(+) Using adoptive cell transfer to treat advanced cancer

Challenge

Approximately 1.6 million people are diagnosed with cancer each year, and one third of those will die from the disease within five years. In particular, patients with advanced, metastatic cancer face limited treatment options and low survival rates. Immunotherapy—the use of the patient's own immune system to fight disease—may prove to be a new option.

Advance

[Steven A. Rosenberg, M.D., Ph.D.](#), and colleagues pioneered the use of adoptive cell transfer, an immunotherapy treatment in which infiltrating immune cells are removed from a tumor, activated in vitro, and then returned to the patient.

Impact

This approach has led to the regression of metastatic cancer in patients with melanomas, sarcomas, and lymphomas, in many cases resulting in long-term survival for people with complex and often refractive tumor types. Furthermore, these advances have helped to launch the field of immunotherapy for the treatment of cancer and chronic infection.

Publications

Rosenberg SA, Yang JC, Sherry RM, Kammula US, Hughes MS, Phan GQ, Citrin DE, Restifo NP, Robbins PF, Wunderlich JR, Morton KE, Laurencot CM, Steinberg SM, White DE, Dudley ME. [Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy](#). *Clin Cancer Res*. 2011;17(13):4550-7.

Morgan RA, Dudley ME, Wunderlich JR, Hughes MS, Yang JC, Sherry RM, Royal RE, Topalian SL, Kammula US, Restifo NP, Zheng Z, Nahvi A, de Vries CR, Rogers-Freezer LJ, Mavroukakis SA, Rosenberg SA. [Cancer regression in patients after transfer of genetically engineered lymphocytes](#). *Science*. 2006;314(5796):126-9.

Dudley ME, Wunderlich JR, Robbins PF, Yang JC, Hwu P, Schwartzentruber DJ, Topalian SL, Sherry R, Restifo NP, Hubicki AM, Robinson MR, Raffeld M, Duray P, Seipp CA, Rogers-Freezer L, Morton KE, Mavroukakis SA, White DE, Rosenberg SA. [Cancer regression and autoimmunity in patients after clonal repopulation with antitumor lymphocytes](#). *Science*. 2002;298(5594):850-4.

2000(+): From hormone to pharmaceutical: lipodystrophy

Challenge

Lipodystrophy is a rare disease in which patients lack body fat and fat-derived hormones, such as leptin. Generalized lipodystrophy results in extreme forms of diabetes, insulin resistance, triglyceride elevation, and fatty liver disease, all of which complicate treatment and can lead to significant morbidity and mortality.

Advance

The first fat-derived hormone, leptin, was discovered in 1994. Since 2000, IRP researchers from the [National Institute of Diabetes and Digestive and Kidney Diseases \(NIDDK\)](#), including [Phillip Gorden, M.D.](#), and [Rebecca J. Brown, M.D., M.H.Sc.](#), have treated more than 100 lipodystrophy patients with leptin replacement therapy, resulting in dramatic improvements in diabetes, lipid levels, and quality of life.

Impact

Based on these clinical studies, metreleptin (Myalept), the first recombinant leptin analog, was approved by the FDA in 2014 to treat patients with generalized lipodystrophy. Targeted treatment of leptin deficiency in lipodystrophy represents a major medical advance in the treatment of an unusual and otherwise difficult-to-treat disease.

Publications

Oral EA, Simha V, Ruiz E, Andewelt A, Premkumar A, Snell P, Wagner AJ, DePaoli AM, Reitman ML, Taylor SI, Gorden P, Garg A. [Leptin-replacement therapy for lipodystrophy](#). *N Engl J Med*. 2002 Feb 21;346(8):570-8.

Chong AY, Lupsa BC, Cochran EK, Gorden P. [Efficacy of leptin therapy in the different forms of human lipodystrophy](#). *Diabetologia*. 2010 Jan;53(1):27-35.

Chan JL, Lutz K, Cochran E, Huang W, Peters Y, Weyer C, Gorden P. [Clinical effects of long-term metreleptin treatment in patients with lipodystrophy](#). *Endocr Pract*. 2011 Nov-Dec;17(6):922-32.

Gorden P, Zadeh ES, Cochran E, Brown RJ. [Syndromic insulin resistance: models for the therapeutic basis of the metabolic syndrome and other targets of insulin resistance](#). *Endocr Pract*. 2012 Sep-Oct;18(5):763-71.

1996: Dissecting good from bad with laser-capture microdissection

Challenge

Due to the mixture of cell types in a tumor biopsy, the ability to separate the different cells in order to study them discretely has been a long-standing problem in research.

Advance

IRP scientists led by [Michael R. Emmert-Buck, M.D., Ph.D.](#), [William M. Bonner, Ph.D.](#), and [Lance Liotta, M.D., Ph.D.](#), invented laser-capture microdissection (LCM) to rapidly and precisely select specific cells from a biopsy sample. Using a low-energy laser beam and special transfer film, LCM enables researchers to isolate normal, precancerous, and cancer cells for analysis.

Impact

This novel technology provides a solution to the problem of isolation and purification of distinct cells within a given tissue sample. LCM has become a well-established research tool used throughout the world, and has been enhanced and expanded into many new biomedical applications.

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Publications

Emmert-Buck MR, Bonner RF, Smith PD, Chuaqui RF, Zhuang Z, Goldstein SR, Weiss RA, Liotta LA. [Laser capture microdissection](#). *Science*. 1996 Nov 8;274(5289):998-1001.

.....

1994(+): IL-15: Taking an immunotherapy from bench to bedside

Challenge

Cytokines are a class of proteins that regulate signaling in the immune system. Since the 1970s, scientists have worked to better understand the large and complex family of cytokine molecules, in hopes of harnessing them to more effectively combat cancer and other diseases.

Advance

IRP researchers led by [Thomas Waldmann, M.D.](#), co-discovered the cytokine IL-15 and revealed its powerful role in triggering a cascade of tumor-fighting immune system cells. The lab demonstrated that IL-15's unique properties made it a potentially better immunotherapy than IL-2, a related protein in clinical use today.

Impact

Dr. Waldmann's team then translated their observations from the research bench to the clinic by initiating the first clinical trials in humans using the cytokine as a cancer therapy. IL-15 is now being tested to treat patients with metastatic malignant melanoma and renal cell cancer. IL-15 has also shown promise in molecular vaccines, which could represent a major advance in treating cancer and autoimmune disorders such as AIDS.

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Publications

Bamford RN, Grant AJ, Burton JD, Peters C, Kurys G, Goldman CK, Brennan J, Roessler E, Waldmann TA. [The interleukin \(IL\) 2 receptor beta chain is shared by IL-2 and a cytokine, provisionally designated IL-T, that stimulates T-cell proliferation and the induction of lymphokine-activated killer cells](#). *Proc Nat Acad Sci U S A*. 1994 May 24;91(11):4940-4.

Waldmann TA, Lugli E, Roederer M, Perera LP, Smedley JV, Macallister RP, Goldman CK, Bryant BR, Decker JM, Fleisher TA, Lane HC, Sneller MC, Kurlander RJ, Kleiner DE, Pletcher JM, Figg WD, Yovandich JL, Creekmore SP. [Safety \(toxicity\), pharmacokinetics, immunogenicity, and impact on elements of the normal immune system of recombinant human IL-15 in rhesus macaques](#). *Blood*. 2011 May 5;117(18):4787-95.

Waldmann TA, Conlon KC, Stewart DM, Worthy TA, Janik JE, Fleisher TA, Albert PS, Figg WD, Spencer SD, Raffeld M, Decker JR, Goldman CK, Bryant BR, Petrus MN, Creekmore SP, Morris JC. [Phase 1 trial of IL-15 trans presentation blockade using humanized Mikβ1 mAb in patients with T-cell large granular lymphocytic leukemia](#). *Blood*. 2013 Jan 17;121(3):476-84.

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Symptoms and Manifestations

2012: Exposing “silent” heart attacks through novel imaging techniques

Challenge

Each year, about 1.2 million people in the U.S. have heart attacks, but not all heart attacks are visible with electrocardiography (EKG). Rapid and accurate methods to detect and manage “silent” heart attacks are needed to speed diagnosis and ensure timely treatment.

Advance

IRP scientists led by [Andrew E. Arai, M.D.](#), pioneered the use of non-invasive magnetic resonance imaging (MRI) to accurately detect and respond to unrecognized myocardial infarctions.

Impact

For the first time, physicians are able to detect, monitor, and treat heart attacks that patients may not even know had occurred. Early intervention in this type of cardiac damage can reduce the likelihood of subsequent cardiac events, including heart failure.

Publications

Schelbert EB, Cao JJ, Sigurdsson S, Aspelund T, Kellman P, Aletras AH, Dyke CK, Thorgeirsson G, Eiriksdottir G, Launer LJ, Gudnason V, Harris TB, Arai AE. [Prevalence and Prognosis of Unrecognized Myocardial Infarction Determined by Cardiac Magnetic Resonance in Older Adults](#). *JAMA*. 2012;308(9):890-896.

2012: Open your eyes to the power of image-based online searching

Challenge

Illustrations in medical literature contribute greatly to understanding complex biomedical concepts—for researchers, scientists, and the lay public alike. However, bibliographic databases are mostly text-based; hence the need for systems that deliver citations enriched by visual material, for example, radiographic images, photographs, sketches, graphs, or charts.

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2010: The Teaching Tool: A digital cervix for colposcopists

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